

LIVER STRUCTURE AND FUNCTION



a



b



c



d



e



f



g



h

Frontispiece : Pioneers in the study of hepatic structure and function a Francis Glisson (1597-1677) of London described the capsule of the liver and the portal circulation b Marcello Malpighi (1628-1694) of Bologna described the microscopic appearance of the liver c René Theophile Hyacinthe Laennec (1781-1826) of Paris coined the term *cirrhosis* d Karl von Rokitansky (1804-1878) of Vienna described acute yellow atrophy e Claude Bernard (1813-1878) of Paris demonstrated the endocrine role of the liver f A. A. Hijmans van den Bergh (1869-1943) of Utrecht initiated the study of bile pigment metabolism g Ludwig Aschoff (1866-1942) of Freiburg described the reticuloendothelial system h Hans Eppinger (1879-1946) of Vienna systemized liver diseases by clinical pathologic correlations (Figures a to g from the portrait collection of the Northwestern University Medical School Library)

LIVER: STRUCTURE AND FUNCTION

Hans Popper, M D, Ph D

Director Department of Pathology The Mount Sinai Hospital Professor of Pathology College of Physicians and Surgeons Columbia University New York Formerly Director Department of Pathology Cook County Hospital Scientific Director Hektoen Institute for Medical Research of the Cook County Hospital Professor of Pathology Northwestern University Medical School Chicago

Fenton Schaffner, M S, M D

Co chairman Department of Medicine Woodlawn Hospital Research Associate Hektoen Institute for Medical Research of the Cook County Hospital Instructor in Medicine Northwestern University Medical School Chicago

The Blakiston Division
McGraw Hill Book Company, Inc
New York Toronto London 1957

LIVER STRUCTURE AND FUNCTION

Copyright © 1957 by the McGraw Hill Book Company Inc. Printed in the United States of America. All rights reserved. This book or parts thereof may not be reproduced in any form without permission of the publishers.
Library of Congress Catalog Card Number 56-7566

*To our patient wives for their enthusiastic help and understanding and to
our children, asking forgiveness for the many long hours away from them*

PREFACE

A disease is understood only if the functional derangement can be clearly associated with the morphologic changes observed during life or on the autopsy table. Introduced by the founders of present-day medicine, this is the recognized credo of students of human illness. Despite the efforts of clinicians and pathologists, the task of correlating the clinical manifestations of liver diseases, the functional derangements as recognized in the laboratory, and the morphologic alterations remains unfinished.

The basic functions of some organs, such as the kidney, are well established. Clinical tests have been devised to measure them, the results of which can be well correlated with the anatomic lesions and clinical findings. The basic functions of the liver are not so well understood, and few tests are available to measure them. Furthermore, the functional alterations resulting from many anatomic changes are still unexplained. Consequently, a classification of basic hepatic disorders can be made only on a descriptive or etiologic basis.

Each patient with liver disease presents anew the problem of correlation between disturbed function and structure. Our present-day fragmentary knowledge has to be applied to each case individually—appraisal cannot rest upon well established associations. The practicing physician will need what little correlated knowledge is available for the diagnosis and management of hepatic diseases. This book attempts to assemble current concepts of hepatic structure and function for the benefit of the physician. Emphasis is placed upon the basis, the method, and the practical application of each of the so-called liver function tests. The diseases are classified on the basis of experience with liver biopsies. Finally, the central position of the liver, anatomically as well as metabolically, suggests a discussion of its relation to other organs as well as its response to external stresses.

Despite the title, which may imply an academic scope, only those aspects of hepatic physiology and pathology which have practical significance will be considered. Other aspects will be excluded, possibly because of lack of foresight. Since so many physiologic processes are represented in the liver, such restraint is necessary to avoid an encyclopedic treatise on general physiology and biochemistry. It also appears unwise to present the clinical features or therapy of a large number of diseases with the excuse that the liver may also be involved. In general, clinical features which are obvious and well described in standard textbooks of medicine are omitted in order to focus interest on the crucial point of correlation of hepatic function and structure.

The chapter divisions follow the modern trend of emphasizing pathophysiologic phenomena rather than diseases. The disease entities are therefore considered as examples of these phenomena; several of which may be involved in a single disease. Moreover, the normal function and structure, being more soundly established, are discussed in considerable detail, whereas the pathologic function and structure are considered in a broader sense. Thus references to basic phenomena do not complicate the descriptions of disease processes—the interested reader is referred to the preceding chapters.

The proper place for the discussion of the so-called liver function tests was not easily decided upon. If the tests were based on a clear understanding of hepatic physiology

PREFACE

the discussion concerning them would logically follow the chapter on normal function. At present however the principles of the hepatic function tests touch only the fringes of physiology. The approach today is still elementary and subject to change. The tests in general reflect pathologic phenomena without identifying their underlying cause. It therefore seems appropriate to discuss the tests as a basis for diagnosis with the object of establishing a usable system rather than as an appendix to the section on physiology.

This book has been made possible by the generous support, helpful criticisms and personal efforts of many persons. Dr. Karl A. Meyer, the medical superintendent of the Cook County institutions and president of the Hektoen Institute for Medical Research of the Cook County Hospital, was a constant source of encouragement and placed at our disposal the facilities of the Cook County Hospital with its laboratories and affiliated institutions. Heartfelt thanks are due to Dr. Samuel J. Hoffman, the executive director of the Hektoen Institute, who not only offered invaluable friendly advice but also generously assisted in overcoming innumerable difficulties throughout the writing of this book.

We are deeply obliged to many of our colleagues who read the manuscript or parts of it and offered very helpful suggestions and corrections: Drs. Sheldon S. Waldstein, Richard B. Terry, Jesus de la Hueraga, Geza C. Kopstein, Alvin Dubin, Irving A. Friedman, and Isidore Snapper deserve special mention. We wish to express our appreciation to the many younger members of the clinical staff of the hospital who uncovered the clinical material and performed many of the biopsies, and to the staff of the department of pathology, whose heavy workload was increased by the collection of material for this book. Much help was provided by Dr. Paul B. Szanto, not only in collecting material but also in offering valuable criticism of the manuscript, which he carefully read. Further stimulation came from the many coworkers with varied fields of interest at the Hektoen Institute who joined in the endeavor to correlate hepatic function and structure. The experiences and observations of Drs. Elias Farber, Franklin de la Hueraga, Koch Weser, Kozoll, Meyer, Steigmann, Szanto, Terry, Volk, and Waldstein, as well as the biochemical analyses of Dubin and Dyniewicz, deserve special recognition. Our staff photographer, Harold L. Miller, was untiring and enthusiastic in his efforts, extending through many years, to provide the pictures used. Angela Bartenbach spent much time in her skillful execution of many of the drawings.

The authors wish to thank those who permitted the reproduction of illustrations published elsewhere, particularly Drs. Hans Elias and Frank Netter. We are indebted to Elizabeth F. Carr, Anna A. Carr, and Georgia Price of the Northwestern University Medical Library for the careful check they made of the references. Thanks are due to the several secretaries who faithfully did the necessary typing.

We feel a sense of obligation to the Josiah Macy, Jr. Foundation and the members and guests of the Conference on Liver Injury for the inspiration they provided one of us who was privileged to attend the Conference.

Many of the original conclusions in this book are based on the study of specimens which friends and colleagues all over the world have sent to our laboratory for study. We use this opportunity to acknowledge our gratitude to them.

Much of the original work upon which this book is based was carried out with the aid of grants generously given by the Jerome D. Solomon Memorial Research Foundation and also by the National Institutes of Health of the United States Public Health Service and the Committee on Scientific Research of the American Medical Association.

*Hans Popper
Fenton Schaffner*

CONTENTS

<i>Preface</i>	vii
<i>Introduction</i>	1
Part I Normal Structure and Function	
1 Structural Principles of the Liver	7
2 Methods of Study of Structure	9
<i>Gross Inspection</i> 9	
<i>Microscopic Study</i> 9	
<i>Cytochemical Analysis</i> 12	
<i>Chemical Analysis</i> 12	
3 Structure of the Hepatic Cell	14
<i>Arrangement of Hepatic Cells</i> 14	
<i>Cytoplasm</i> 14	
<i>Nucleus</i> 21	
4 Metabolic Function of the Liver the Metabolic Pool and Metabolic Interrelationships	24
<i>The Metabolic Pool</i> 24	
<i>Energy Provision</i> 25	
<i>Metabolic Interrelations of Fatty Acids Carbohydrates and Proteins</i> 27	
<i>Addendum</i> 733	
5 Metabolic Function of the Liver Carbohydrate and Lipid Metabolism	30
<i>Carbohydrate Metabolism</i> 30	
<i>Lipid Metabolism</i> 32	
6 Metabolic Function of the Liver Protein Metabolism	40
<i>Anabolism (Protein Synthesis)</i> 40	
<i>Catabolism</i> 44	
<i>Addendum</i> 733	
7 Metabolic Function of the Liver Enzymes	46
<i>Phosphatases</i> 46	
<i>Esterases</i> 49	
<i>Amylase</i> 50	
<i>Other Enzymes</i> 50	
<i>Addendum</i> 733	
8 Metabolic Function of the Liver Vitamins Minerals and Water	52
<i>Vitamin Metabolism</i> 52	
<i>Mineral Metabolism</i> 59	
<i>Water Metabolism</i> 62	
<i>Addendum</i> 733	
9 Metabolic Function of the Liver Bile Acid Metabolism	63
<i>Addendum</i> 734	
10 Metabolic Function of the Liver Transformations (Detoxification)	67
11 Blood and Bile Pigment Metabolism and the Role of the Liver	70
<i>Addendum</i> 734	

CONTENTS

12	Excretory Function of the Liver	80
	<i>Bile Formation</i> 80	
	<i>Dye Excretion</i> 85	
	<i>Addendum</i> 734	
13	Function of the Nucleus of the Hepatic Cell	87
	<i>Adult or Replacement Growth</i> 87	
	<i>Regeneration</i> 89	
	<i>Addendum</i> 734	
14	Sinusoids	94
	<i>Structural Characteristics of the Hepatic Sinusoids</i> 94	
	<i>Functional Characteristics of the Hepatic Sinusoids</i> 100	
	<i>Addendum</i> 734	
15	Structure of the Biliary System	103
	<i>Bile Canaliculi</i> 103	
	<i>Bile Ductules</i> 103	
	<i>Intrahepatic Bile Ducts</i> 106	
	<i>Extrahepatic Bile Ducts</i> 106	
	<i>Termination of the Common Duct</i> 108	
	<i>Gallbladder</i> 110	
16	Function of the Biliary System	113
	<i>Intrahepatic Bile Ducts and Biliary Pressure</i> 113	
	<i>Gallbladder</i> 113	
	<i>Extrahepatic Bile Ducts</i> 116	
	<i>Sphincter of Oddi</i> 116	
	<i>Interrelation between Gallbladder and Sphincter of Oddi</i> 117	
	<i>Regeneration of Bile Ductules and Ducts</i> 119	
17	Structure of Hepatic Blood Vessels	122
	<i>The Hepatic Artery</i> 122	
	<i>The Portal Vein</i> 127	
	<i>The Hepatic Vein</i> 133	
	<i>Structural Principle of the Vascular Tree</i> 135	
18	Function of Hepatic Blood Vessels	137
	<i>Portal Vein</i> 139	
	<i>Hepatic Artery</i> 143	
	<i>Hepatic Vein</i> 145	
	<i>Differences in Composition of Blood in the Various Vessels</i> 145	
	<i>Regulation of Hepatic Blood Flow</i> 146	
	<i>Addendum</i> 734	
19	Lymphatic Vessels Tissue Spaces Innervation and Stroma of the Liver	149
	<i>Lymphatic Vessels and Tissue Spaces</i> 149	
	<i>Innervation of the Liver</i> 151	
	<i>Stroma</i> 154	
20	The Liver as a Whole	157
	<i>The Liver Lobule</i> 157	
	<i>Gross Anatomy</i> 160	
	<i>Embryology</i> 163	
	<i>Malformations and Malpositions</i> 169	
	<i>Agonal and Postmortal Changes</i> 173	
	<i>Addendum</i> 735	

Part II Pathologic Phenomena in the Hepatobiliary System

21	Jaundice	179
	<i>Classification of Jaundice According to Existing Theories</i> 179	
	<i>Criticism of Existing Theories</i> 181	

CONTENTS

	<i>Proposed Classification of Jaundice</i>	185
	<i>Jaundice with Impairment of Bile Flow</i>	187
	<i>Relation between Serum and Tissue Bilirubin (Visible Jaundice)</i>	195
	<i>Addendum</i>	735
22	Hepatocellular Degeneration and Necrosis Structural Alterations	200
	<i>Hepatocellular Degeneration</i>	200
	<i>Necrosis</i>	205
23	Hepatocellular Degeneration and Necrosis Functional Alterations	215
	<i>Chemical Changes in Serum and Urine in Hepatic cell Degeneration</i>	215
	<i>Clinical Manifestations of Hepatic Insufficiency</i>	219
	<i>Addendum</i>	735
24	Cholestasis	223
	<i>Morphologic Appearance</i>	225
	<i>Changes in Other Organs</i>	237
	<i>Functional Consequences</i>	237
25	Inflammation	240
	<i>Edema</i>	240
	<i>Proliferation of Kupffer Cells and Portal Histiocytes</i>	241
	<i>Focal Necrosis Intralobular Granuloma</i>	241
	<i>Portal and Periportal Inflammation</i>	242
	<i>Cholangiolitis</i>	245
	<i>Intrahepatic Purulent Cholangitis</i>	246
	<i>Extrahepatic Cholangitis</i>	248
26	Fatty Metamorphosis	249
	<i>Morphology of Fatty Metamorphosis</i>	249
	<i>Etiology of Fatty Metamorphosis</i>	252
	<i>Functional Manifestations</i>	253
	<i>Sequelae</i>	254
	<i>Addendum</i>	735
27	Increase of Connective Tissue (Fibrosis)	255
	<i>Forms of Fibrosis</i>	255
28	Structural Features of Cirrhosis	262
	<i>Morphogenetic Pathways</i>	263
	<i>Processes Common to All Types of Cirrhosis</i>	272
	<i>Classification of Cirrhosis</i>	278
	<i>Addendum</i>	735
29	Functional Changes in Cirrhosis	280
	<i>Review of Basic Functional Alterations</i>	280
	<i>Relation of Structural and Functional Alterations</i>	280
	<i>Portal Hypertension</i>	283
	<i>Ascites</i>	292
	<i>Addendum</i>	736
30	Gallbladder Syndromes	298
	<i>Biliary Dyskinesia</i>	298
	<i>Gallstone Formation (Cholelithiasis)</i>	299
	<i>Cholecystitis</i>	304
	<i>Interdependence of Gallbladder Syndromes</i>	308
	<i>Addendum</i>	736
 Part III: Clinical Study of Hepatic Function and Structure		
31	Introduction to the Hepatic Tests	313
32	Major Serum protein Fractions	315
	<i>Total Serum Protein</i>	315
	<i>Fractionation of Serum Proteins</i>	316

CONTENTS

	<i>Serum Albumin</i>	318
	<i>Alpha Globulin</i>	319
	<i>Beta Globulins</i>	319
	<i>Gamma Globulin</i>	319
	<i>Total Serum Globulin</i>	321
	<i>Albumin/Globulin Ratio</i>	322
	<i>Fibrinogen</i>	322
33	Nonspecific Serum protein Reactions Flocculation or Turbidity Tests <i>Coordinated Use of Flocculation Tests</i>	323 331
34	Miscellaneous Tests Concerning Protein and Nitrogen Metabolism <i>Tests Related to Protein Catabolism</i>	333 337
35	Tests Referring to Enzymes Carbohydrates and Lipids <i>Tests Based on Enzymes</i> <i>Tests Based on Carbohydrate Metabolism</i> <i>Tests Concerning Carbohydrate Intermediates</i> <i>Tests Based on Fat Metabolism</i> <i>Addendum</i>	340 340 344 347 347 736
36	Tests Based on Bile Pigment Metabolism <i>Serum Bilirubin</i> <i>Bilirubin and Urobilinogen in Urine Feces and Bile</i> <i>Porphyrins</i>	354 354 357 364
37	Miscellaneous Tests <i>Tests Based on Bile Acid Metabolism</i> <i>Tests Concerning Vitamin A Minerals and Electrolytes</i> <i>Transformation Tests</i> <i>Dye excretion Tests</i> <i>Addendum</i>	365 365 366 367 370 736
38	Roentgenologic Visualization of the Liver and Biliary Tract and Duodenal Drainage <i>Duodenal Drainage</i> <i>Addendum</i>	374 374 736
39	Liver Biopsy <i>Methods</i> <i>Applications of Liver Biopsy</i>	379 379 383
 <i>Part IV Diffuse Diseases of the Liver</i>		
40	Classification and Nomenclature of Hepatic Diseases	389
41	Toxic Hepatic Injury <i>Experimental Hepatic Injury</i> <i>Etiologic Factors in Human Toxic Injury</i> <i>"Allergic" Cholangiolitis</i> <i>Nonspecific Reactive Hepatitis</i> <i>Toxic Hepatic Necrosis</i> <i>Addendum</i>	391 391 393 403 404 407 736
42	Hepatic Injury from Infectious Agents Classification Etiology and Epidemiology of Viral Hepatitis <i>Viral Hepatitis—Etiology and Epidemiology</i> <i>Addendum</i>	413 413 414 737
43	Hepatic Injury from Infectious Agents Acute Viral Hepatitis <i>Clinical Manifestations</i> <i>Laboratory Findings</i> <i>Addendum</i> <i>Structural Alterations</i>	422 422 425 737 426

CONTENTS

44	Hepatic Injury from Infectious Agents Chronic Viral Hepatitis Types of Protracted Hepatitis 440 Addendum 737	439
45	Hepatic Injury from Infectious Agents Diseases Other Than Viral Hepatitis Yellow Fever Hepatitis 455 Other Types of Hepatitis Produced by Viruses 456 Leptospirosis Hepatitis (Weil's Disease) 457 Relapsing Fever 458 Malarial Hepatitis 458 Leishmaniasis 459 Trypanosomiasis 459	454
46	Diffuse Hepatic Diseases with Cholestasis of Unknown Etiology Cholangiolitis and Pericholangiolitis 462 Addendum 737	460
47	Hepatic Injury from Extrahepatic Biliary Obstruction Simple Cholestasis 468 Biliary Hepatitis 469 Chronic Biliary Hepatitis (Biliary Fibrosis) 469 Infected Biliary Hepatitis 471 Chronic Infected Biliary Hepatitis (Secondary Biliary Cirrhosis) 472 Types of Cirrhosis Related to Cholestasis 472 Addendum 738	468
48	Congestive Hepatic Injury Experimental Studies 473 Human Hepatic Injury from Congestion 474 Addendum 738	473
49	Hepatic Injury from Disturbed Circulation and Anoxia Hepatic Necrosis from Shock 482 Hepatic Congestion in Thyrotoxicosis 483 Hepatic Necrosis in Eclampsia 483 Hepatocellular Degeneration from Hemolysis 499	482
50	Nutritional Hepatic Injury Experimental and Etiologic Considerations Nutritional Hepatic Injury in Animals 493 Hepatic Injury from Dietary Imbalance or Multiple Factors 496 Effects of Alcohol on the Liver 501 Addendum 738	492
51	Nutritional Hepatic Injury Clinical Entities Fatty Liver-cirrhosis Syndrome from Malnutrition 504 Addendum 738	503
52	Review of the Clinical Problems and Classification of Cirrhosis Laennec's Cirrhosis 520 Morphogenetic Classification 523 Etiologic Classification 523 Functional therapeutic Classification 524 Proposed Nomenclature 531 Differential Diagnosis of Cirrhosis by Laboratory Tests 531 Addendum 738	520
53	Metabolic Hepatic Injury Iron-storage Diseases 532 Hepatolenticular Degeneration (Wilson's Disease) 540 Glycogen storage Disease 542 Galactosemia 543 Lipid storage Diseases in the Liver 544	532

CONTENTS

	<i>Hepatic Amyloidosis</i>	545
	<i>Addendum</i>	738
	<i>Focal Diseases of the Liver</i>	
	<i>Granulomatous Diseases of the Liver</i>	551
	<i>Hepatic Tuberculosis</i>	551
	<i>Hepatic Sarcoidosis</i>	556
	<i>Hepatic Brucellosis</i>	559
	<i>Hepatic Syphilis</i>	562
	<i>Hepatic Granulomas in Various Diseases</i>	564
	<i>Fungus Infections of the Liver</i>	565
	<i>Differential Diagnosis of Hepatic Granulomas</i>	567
	<i>Addendum</i>	739
55	<i>Parasitic Diseases of the Liver</i>	569
	<i>Protozoan Infestations of the Liver</i>	569
	<i>Helminth Infestations of the Liver</i>	572
	<i>Arthropods in the Liver</i>	578
	<i>Addendum</i>	739
56	<i>Vascular Diseases and Abscesses of the Liver</i>	579
	<i>Vascular Diseases of the Liver</i>	579
	<i>Liver Abscesses</i>	583
	<i>Part VI Tumors of the Liver and Biliary Tree</i>	
57	<i>Hamartomas and Benign Tumors</i>	587
	<i>Hepatic Hamartomas</i>	587
	<i>Benign Tumors</i>	592
	<i>Addendum</i>	739
58	<i>Primary Hepatic Carcinoma</i>	593
	<i>Experimental Carcinogenesis</i>	593
	<i>Human Primary Hepatic Carcinoma</i>	599
59	<i>Carcinoma of the Biliary Passages Nonepithelial Tumors and Metastatic Tumors of the Liver</i>	613
	<i>Carcinomas of the Biliary Passages</i>	613
	<i>Nonepithelial Tumors of the Liver and Biliary Tract</i>	616
	<i>Metastatic Tumors in the Liver</i>	616
	<i>Addendum</i>	739
	<i>Part VII Internal and External Environment and the Liver</i>	
60	<i>Relation of Liver to Spleen and Hematopoietic System</i>	623
	<i>Hepatolienal Relationships</i>	623
	<i>Relation between Liver and Hematopoietic System</i>	624
	<i>Effect of the Liver on the Hematopoietic System</i>	627
	<i>Addendum</i>	739
61	<i>Relation of the Liver to the Gastrointestinal Tract and Pancreas</i>	630
	<i>Relation between the Liver and the Gastrointestinal Tract</i>	630
	<i>Relation between the Liver and Exocrine Pancreas</i>	632
	<i>Addendum</i>	739
62	<i>Relation of the Liver to the Endocrine Glands</i>	635
	<i>Pituitary Gland</i>	635
	<i>Adrenal Gland</i>	638
	<i>Relation between the Pancreatic Islands and the Liver</i>	639
	<i>Relation between the Liver and Sex Organs</i>	643
	<i>Addendum</i>	739

CONTENTS

63	Relation of Liver to kidney Cardiovascular System Skeleton and Central Nervous System	647
	<i>Hepatorenal Relationships</i> 647	
	<i>Relation between the Liver and the Cardiovascular System</i> 651	
	<i>Relation between the Liver and the Skeletal System</i> 651	
	<i>Relation between the Liver and the Central Nervous System</i> 652	
	<i>Addendum</i> 739	
64	Hepatic Response to Stress	654
	<i>Traumatic Hepatic Injury</i> 654	
	<i>Severe Trauma Not Involving the Liver</i> 655	
	<i>Hypothermia</i> 655	
	<i>Ionizing Radiation</i> 656	
	<i>Hypersensitivity</i> 658	
 Part VIII Appendix		
	Principles of Diagnosis of Liver Disease Based on Coordinated Use of Functional and Structural Observations	661
	<i>Application of Hepatic Tests and Liver Biopsy as Ancillary Procedures in Clinical Problems</i> 664	
	 <i>Bibliography</i>	671
	<i>Addendum</i>	733
	<i>Index</i>	741

Introduction

The shape of the liver aroused interest several thousand years before the birth of Christ. A Babylonian model of the liver kept in the British Museum shows segmentation which matches well the results of modern injection techniques (Fig. 1). The shape of the liver in sacrificial animals was thought to bear omen about the future, and the haruspex or diviner inspecting the viscera of such animals was believed to learn much from the size of the right or left lobe. The shape of the liver was consulted before the warrior went to

the Theban War (Fig. 2). An Etruscan liver model found in central Italy shows a similar, although less elaborate shape. Little curiosity existed to explore the relation of this shape to the health of the animal itself, and a similar approach was made to human necropsy specimens. Autopsies were performed by the Egyptians in which the heart weight was recorded but relatively little concern was exhibited for correlation between the shape of the organs and their function. All through the older necropsy studies, including the older

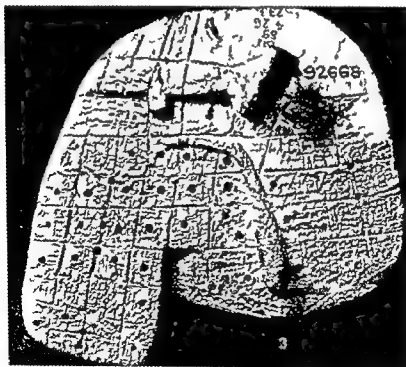


FIG. 1. Clay model of sheep liver made by Babylonian priests 2000 B.C. preserved in the British Museum, London. (From the portrait collection of North Western University Medical School Library.)



FIG. - Diviner (haruspex) showing the liver of a sacrificial animal to Adrastus a Greek warrior departing for the Theban War. Drawn on a Greek vase (From the portrait collection of Northwestern University Medical School Library)

German or Italian ones the shapes of the altered organs were in the foreground of interest of the physicians

As biological knowledge improved the study of structure became more elaborate. Analytical data obtained by more and more exact measurements became the goal of the different biologic disciplines such as anatomy, physiology, biochemistry and biophysics. The cellular pathology of Rudolf Virchow opened the finer structural elements of the body to investigation. This analysis of altered microscopic and even submicroscopic structure for its own purpose is best exemplified in the fundamentalist approach especially found in the German school of pathology. Ricker as the most articulate spokesman of this line of thinking considered pathology as a natural science in its own right its aim being to study the structural changes of disease for its own purpose with little more concern for the clinical implications than the Babylonian or Greek haruspices showed when they studied the shape of the liver to predict the future.

A synthetic approach to pathology the attempt to correlate structure and function or in other

words to relate the findings of the autopsy table with clinical observation came into flower only in the amphitheatres of the later classic Italian schools. Two men contributed much to this development in pathology. Anthony Benivieni whose *De abditis nonnullis ac mirandis morborum et sanationum causis* (About Many Unusual and Miraculous Causes of Diseases and Cures) appeared in 1507 was a forerunner of Giovanni Morgagni whose *De sedibus et causis morborum per anatomen indagatis* (About the Sites and Causes of Disease Investigated by Anatomy) appeared in 1761. Many physicians from all over the Western world came to the Italian amphitheatres and in Bologna autopsies were performed under the inscription which we today proudly exhibit in the amphitheater of the Department of Pathology of Cook County Hospital: *Hic locus est ubi mors gaudet succurrere vitae* (This is the place where death enjoys helping life). The approach of having structure and function correlated by an investigator who was both clinician and pathologist is best exemplified by the great leaders of the English and French schools of the later eighteenth and nineteenth centuries men such as Hodgkin

Bright Laennec and others who went from the autopsy table into the wards. This approach was expressed in the writings of the Austrian Karl Rokitansky. He did not neglect to make most careful anatomical observations yet he also emphasized the correlation with the basic sciences such as chemistry for understanding pathologic processes not for obtaining analytical data for its own sake. In contrast to the fundamental approach pathology became a correlative or integrative science differing from the analytical biologic sciences by having no technique but an approach of its own using all morphologic chemical and other data for correlation with the clinical picture and with laboratory findings during life. The correlation may be based upon observations on an individual patient or it may be the result of statistical evaluation of observations on many patients. From several possible answers the one best suited has to be selected. The conclusion is to be considered tentative a working hypothesis to be proved by further observations. The pathologist brings his studies on correlation and integration thus differs from the basic scientists in his approach to problems and uses the intuition characteristic of any clinical art.

The problem of correlation has become more and more complex as pathology has advanced from the naked eye observations of the haruspices and the prosectors of the Italian schools to the complex methodology of microscopy submicroscopy histochemistry and histophysics. However the original challenge confronting Beniveni Morgagni Laennec and Rokitansky has remained the same. It confronts the pathologist in his daily work in his clinical service in his teaching and in his research.

The pathology of the liver offers a timely challenge to correlate functional and structural alterations in view of the coincidence of recent advances in physiology biochemistry and anatomy and the opportunity to supplement autopsy findings with biopsy observations on the liver of living patients. For centuries a big gap existed between the morphologic picture of the organ and the clinical and laboratory manifestations of hepatic insufficiency. This is exemplified by the common experience during autopsy on a patient dead of cardiac failure without any signs of hepatic insufficiency to find an almost complete absence of viable hepatic cells. A correlation between function and structure must exist even if we can not see it. The challenge lies in finding it by proper techniques. One of the earliest leaders attempting to fill this gap was Hans Eppinger in Vienna who starting from the morphology of bile canaliculi in jaundice proceeded to become a leading clinician and who throughout his entire life fell back to morphologic study for the evaluation of disturbed function of the liver. Our own attempts to contribute to this problem were stimulated by the inspiration which one of us (H.P.) received in Eppinger's clinic as a young pathologist.

Some of the correlations suggested in this book will possibly be corrected on the basis of further study or improved techniques. Moreover the coincidence of lesions does not necessarily prove their causal relation. Nevertheless attempts at correlation although not removing the necessity for the most thorough morphologic observations should result not only in better understanding of the basis of morphologic alterations and improved knowledge of hepatic disease but also in better interpretations of the various hepatic tests.

PART I

Normal Structure and Function

The liver is composed of small units called lobules in the center of which are hepatic vein branches. In circumscribed areas on the periphery of these lobules (portal spaces or tracts) radicles of the portal vein and the hepatic artery are found. These provide blood which flows through the sinusoids toward the central vein. The sinusoids are modified capillaries with specially adapted endothelial cells, the Kupffer cells. Between the sinusoids, the hepatic cells form a continuous framework of plates or sheets. Between the plates and the capillaries are the tissue spaces in which tissue fluid slowly moves. In man, most of this fluid flows toward the periphery of the lobules. The lymphatic vessels start around the blood vessels and nerves in the portal tracts and also in the central spaces. Between adjacent hepatic cells, bile canaliculi are found through which bile flows toward the portal spaces through collecting ductules. In the portal spaces, these ductules unite and form the smaller bile ducts which combine to form larger ducts finally joining at the hilum of the liver in the extrahepatic ducts. Thus three fluid currents are present in the liver:

1. Blood flowing from the portal space to the center of the lobule
2. Bile flowing from the center toward the periphery
3. Tissue fluids flowing in both directions

The liver contains a number of structural entities each with specific functions and significantly different types of pathologic alterations which will be discussed first from the morphologic and then from the functional aspect. These units are: (1) the hepatic cell, (2) the Kupffer cell, (3) the blood capillaries, (4) the bile canaliculi, (5) the intrahepatic bile ducts, (6) the extrahepatic bile ducts with the gallbladder, (7) the blood vessels,

(8) the lymphatics and connective tissue in the portal spaces continuous with Glisson's capsule, (9) the nerves (Fig. 3).

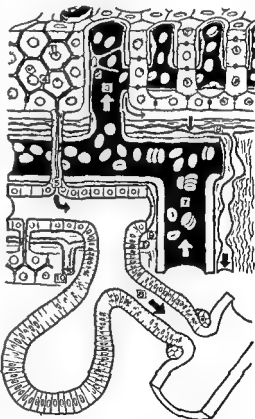


FIG. 3. Basic structures and currents of flow in the liver. (1) hepatic cell, (2) Kupffer cell, (3) sinusoid, (4) bile canaliculus, (5) bile ductule, (6) bile duct, (7) vein, (8) lymphatic vessel, (9) stroma, (10) nerve.

The structural units listed are not necessarily functional units. In the kidney the nephron is a well defined functional unit. In the central nervous system the functional unit is the neuron. The entire heart acts as a unit. The liver as the central chemical factory of the body engages in more diversified activities than any other organ and

the different functions require different functional units. In a few instances mitochondria isolated by ultracentrifugation or liver homogenates can perform certain chemical tasks. For most metabolic processes the intact hepatic cell is necessary. For some metabolic functions however an entire lobule may be needed.

The structure of the liver can be studied by various methods which may often give conflicting results. This has created much confusion and the interpretation of the results and the limitations of the methods require comparison and evaluation. In principle the methods are (1) gross and microscopic study of form (2) chemical and physical analysis of (a) microscopic structures (histochemistry and histophysics) (b) isolated cellular elements (cytochemistry) (c) whole organs. The techniques as applied to the liver are better divided into gross inspection, microscopic study and cytochemical analysis.

GROSS INSPECTION

The conventional gross inspection of the liver has been repeatedly supplemented by injection techniques in which the various vessels of the liver or the bile ducts are injected with India ink or with a 5 per cent solution of gelatin containing such various dyes as prussian blue or carmine [910]. If carmine is used the vascular tree first should be flushed with dilute acetic acid to prevent diffusion of the dye [2631]. Gross inspection can be supplemented by observation under low magnification in incident light or by inspection of thick frozen sections mounted in glycerin using transmitted light. Preparations in which the vessels are injected with barium can be studied roentgenologically [1535]. In addition casts of the vessels can be prepared by injecting them with colored Vinylite or neoprene latex and digesting the organ for 4 days in concentrated hydrochloric acid. The resulting specimens can be inspected grossly or microscopically in incident light [2210, 2631]. Vessels smaller than 30 μ usually do not fill. For the study of drug action on vessels, ace-

tone celluloid solutions have been injected when the liver was still functioning and corrosion preparations have subsequently been made [763].

MICROSCOPIC STUDY

The liver can be studied intravitaly or in tissue preparations by the light microscope, fluorescence microscope, phase microscope, ultraviolet microscope or electron microscope. From a theoretical standpoint microscopic examination of the living liver is far superior to the study of tissue sections prepared by conventional methods (paraffin sections). These sections have been subjected to (1) fixation which denatures the protein and distorts the cellular architecture, (2) embedding which heats the tissue and removes a large part of its original constituents leaving a cooked and distorted skeleton of the original. Despite these justified objections to conventional methods of microscopic analysis, neither vital microscopy nor any of the recent improvements in histological technique has produced results comparable to the vast amount of information derived from routine studies on which almost all our information about liver structure is based.

Vital Microscopy

For the study of living tissue in visible light, a fused quartz rod is placed below the area to be studied to which the rod delivers the light directly [1808, 3463]. Much information on blood flow through the liver has been obtained by this method. To improve visualization of vessels and bile ducts fluorescent dyes have been injected and their flow has been observed with the fluorescence microscope. Observation of fixed specimens following vital microscopic study has been a valuable

4 Damaging causes

- a Infection
- b Trauma if serious
- Emotion
- d Irradiation
- Other abnormalities
 - (1) Cerebral
 - (2) Pulmonary
 - (3) Cardiovascular
 - (4) Renal
 - (5) Malignant tumors may compete for body nourishment

IV STAGES^{8 9 10}

1 GENERAL (see Charts 8, 9 Figs 1, 2)

- 1 The stages of development have been divided into groups as shown in Table 4
- 2 Knowledge of these findings is important in differentiating the normal from the abnormal (see I IV and VI)
- 3 These groups do not always correspond to chronologic age, but are based chiefly on
 - a Height
 - b Skeletal development

TABLE 4 STAGES OF MASCULINE DEVELOPMENT¹⁰

	GROUP 1 PREPUBESCENCE	GROUP 2 INTERMEDIATE PREPUBESCENCE AND PUBESCENCE	GROUP 3 PUBESCENCE	GROUP 4 ADOLESCENCE	GROUP 5 POST ADOLESCENCE	GROUP 6 ADULTHOOD (AFTER 25)
Voice	No change	None or slight change	None or slight change	Changing or changed	Changed	Adult
Breasts	No change	None to slight	May be prominent	Subsided	Absent	Absent
Hair						
Head	Normal	Normal	Normal	Normal	May begin receding	Increased recession
Facial	Absent	Absent	Light slightly pigmented on upper lip	Light beard and mustache	Adult growth	Adult growth
Aural	Absent	Absent	Absent	Absent	Absent	Grows about age 35
Nasal	Absent	Absent	Absent	Absent	Absent	May appear eyebrows may become more bushy
Axillary and pubic	Absent	Slightly pigmented	Sparse but pigmented	Good growth beginning male escutcheon	Adult growth	Adult growth
Body	Absent	None other than down	Few pigmented	Some may be pigmented	Near adult type	May increase
Penis length in cm	3.8	4.5-12	8-15	9-15	10.5-18	10.5-18
Testicular volume in cc	0.3-1.5	4-8	2-70	6-20	8-25	8-25
Prostate	Flat or small	Flat or small	Flat or small	Near adult size	Adult	Adult
Distribution by chronologic age	Years Per Cent		Years Per Cent		Years Per Cent	
	1-11	76	10	2	12	10
	12	44	11	12	13	21
	13	15	12	22	14	26
	14	6	13	28	15	22
			14	20.5	16	11
			15	9	17	7
			16	5	18	7
			17	1.5	20	17
					13	11
					14	27
					15	53
					16	59
					17	39
					18	30
					19	26
					20	21
					21	100

argaffin reticulum fibers (important in the visualization of collapse and its differentiation from fibroplasia) silver impregnations are used according to either Wilder or Gomori in which the black framework as well as its alterations stands out distinctly

FAT STAINS Fat droplets can be demonstrated in frozen sections of unfixed tissue or in tissue fixed (preferably for a short period) in formalin by staining with sudan III or oil red O and related dyes. In paraffin sections they are demonstrable after fixation with osmic acid. This causes the fatty acid to become blackened by the reduction of osmium tetroxide to osmium dioxide. In routine paraffin sections the fat appears as vacuoles. Only when these vacuoles are large are they characteristic for fat. However, even in frozen sections the amount of demonstrable fat droplets depends upon the staining techniques and usually more is found if water soluble dyes are used.

NUCLEIC ACID STAINS Unna Pappenheim's methyl green pyronin stains pentose nucleic acids (PNA) red and the nuclear deoxypentose nucleic acids (DNA) green [368-2059]. This reaction is not specific for PNA since acidic proteins produce a pyroninophilic reaction [4619] and therefore confirmation is required. One method is the digestion with the enzyme ribonuclease the crystalline preparations of which are now free of proteolytic activity [1874]. Cold 10 per cent perchloric acid or hot normal hydrochloric acid specifically removes PNA whereas hot trichloroacetic acid removes all nucleic acids [2474-2948]. After acid hydrolysis DNA stains purple with fuchsin sulfurous acid (Feulgen reaction) supposedly because aldehyde groups are generated.

CARBOHYDRATE STAINS Rapid hydrolysis of hepatic glycogen occurs after death (see Chemical Analysis later in this chapter). This process comes almost to a standstill within a few hours probably because of accumulation of organic acids or binding of inorganic phosphates. Liver tissue which has not been fixed shortly after death may therefore reveal a significant reduction or almost complete disappearance of glycogen. Hepatocellular glycogen also disappears in fixatives if they are not strongly alcoholic (absolute alcohol or Carnoy's solution) or if they are not saturated with glucose—in contrast to glycogen in other locations including the nucleus of the hepatic cell. The frequency with which glycogen can be demonstrated in formalin fixed material especially with the periodic acid routine is surprising. Glycogen can

be stained with iodine. Best's carmine or Schiff's periodic acid routine (PAS). The PAS stain consists of staining of aldehyde groups with fuchsin sulfurous acid after oxidation of saccharides by periodic acid. PAS stains replace the older methods for demonstration of glycogen after identification in control sections in which glycogen has been removed by diastase digestion using saliva or commercial enzymes. The PAS also stains red the mucinous secretion of the interlobular bile ducts as a film lining the lumen and wear and tear pigments fibrin thrombi amebias and fungi especially histoplasma while amyloid shows a poor reaction. The reticulum framework of the liver is less regularly and intensely stained by PAS.

BILE CANALICULUS STAINS In most species bile canaliculi can be visualized with Eppinger's hematoxylin stain Mallory's aniline blue stain or Gomori's alkaline phosphatase stain.

OTHER STAINS The attempt to demonstrate bile pigments is still in the experimental stage. Demonstration of elastic fibers assists in visualization of the portal tracts and is helpful in cirrhosis. For cytologic studies of hematopoietic elements Wolbach's modification of Giemsa stain may be used. Bacteria can be visualized with one of the modifications of the Gram stain such as Goodpasture's stain. With acid fast stains tubercle bacilli can be demonstrated although only exceptionally and also wear and tear pigment and ceroid a pigment occurring in experimental cirrhosis (see Ceroid under Lipogenic Lipotropic Imbalance: Experimental Fatty Liver Cirrhosis Syndrome Chap 50). The metachromasia of amyloid can be elicited with either congo red or methyl violet.

HISTOCHEMICAL REACTIONS Histochemical analysis of various tissue components is a promising field for the future [129-1218]. Alkaline phosphatase appears black with Gomori's stain which is the most widely utilized but, as with all histochemical methods great care and proper controls must be used to avoid artefacts. Of the minerals iron demonstrated with the prussian blue reaction is the most important. Iron can also be demonstrated by microincineration [2974]. Recently radioautographs with radioactive substances have been applied [1027].

Supravital Microscopy

Examination of cells from tissue cultures is usually performed after fixation of the specimens [811-1083]. The distribution of dyes or corpuscular elements is studied after intravenous injection

- d Prediction may vary from all known growth charts
 - (1) Tall children especially
 - (2) When somatic age appears constant with chronologic age

D BONE AGE

- 1 Roentgenograms of
 - a Skull for closure of sutures
 - b Hands and wrists
 - c Iliac crests if radial epiphyses are closed
 - d Other epiphyses if desired
- 2 Estimation
 - a Hands and wrists—comparison with
 - (1) Todd's standards⁴ (see Fig 19)
 - (2) Ossification index of Leonard¹ (see Fig 18)
 - b Iliac crests
 - c Clavicles
 - d 'Ossification sums'⁴ are not practical for routine use
- 3 Comments
 - a Normal variation—1 year
 - b Abnormal range—2 years or more
 - c Advanced bone age, 1 to 2 years—
with greater than average height heralds early onset of puberty
 - d Prediction of final height (see Charts 145 and 146)
 - (1) Useful when bone age is abnormal in children who are
 - (a) Apparently normal and with beginning pubescence
 - (b) Sexually precocious
 - (2) Mark observed height of subject opposite chronologic age which will determine percentile curve (A)
 - (3) Substituting bone age for chronologic age find point where corresponding perpendicular line crosses percentile curve (A above)
 - (4) Read to left of chart for height corresponding to bone age
 - (5) Subtract bone age height from final height on same percentile curve (18 years for girls and 19 years for boys)
 - (6) Add difference to observed height the sum of which may prove to be final height

- (7) If observed height falls beyond curves of chart, suitable interpolation may be made

(8) Example

- (a) Boy with beginning pubescence—chronologic age 9, height 54 in, bone age 12
- (b) Point falls on 90 percentile curve
- (c) Height for bone age on this curve—60 in
- (d) Final height on same curve—71 in
- (e) 71 minus 60 in equals 11 in
- (f) Observed height of 54 in plus 11 in (difference of above) equals 65 in for final height

- (9) Comments on variations in normal growth rate

- (a) Decreased by
 - [1] Illness
 - [2] Serious injury
 - [3] Food deficiencies (including avitaminosis)
- (b) Increased
 - [1] In taller or obese children
 - [2] With earlier onset of puberty (bone age may be so advanced that growth ends sooner)

TABLE 5 USEFUL DATA FOR ESTIMATING BONE AGE AFTER CLOSURE OF RADIAL EPIPHYSES¹⁰

BONE	SEX	APPEARANCE OF OSSIFICATION OR CALCIFICATION YEARS	TIME OF EPIPHYSEAL CLOSURE YEARS
Iliac crests	Male	18 20	21 23
	Female	17 19	21 22
Medial end of clavicles	Male	19 20	23 24
	Female	18 19	22 23
Cartilage of first rib	Male and female	26 27	

- Sexual maturation
- 4 The sum total of these variants (a, b, c above as well as others) has been termed maturity or 'somatic age'
- 5 Final maturity or somatic age
 - a Linear growth has ceased
 - b Skeleton is fully developed
 - c Chronologic age of 25 (average)

V METHODS OF MENSURATION

A MENTAL AGE ¹¹

- 1 Special methods for evaluation are not discussed herein
- 2 Reading age
 - a Spurts in
 - (1) Boys at 10 to 11 years
 - (2) Girls at 9 to 10 years
 - b Late menarche may cause a delay
 - c Family accomplishments are important here
- 3 Achievement is only partially dependent on learning processes
 - a Forcing educational methods is inadvisable
 - b Pacing instruction is better because a child rejects what he is not ready to absorb
 - c Expectancy of accomplishments is conditioned by
 - (1) Sex
 - (2) Total maturity (i.e. summation of all 'ages')
 - (3) Familial trends
- 4 Total growth stability, i.e. physical and mental is not easily altered

B WEIGHT

- 1 Check preferably
 - a On arising
 - b After voiding
 - c Before eating
- 2 Comments
 - a Maintenance of a constant weight in child is equivalent to a loss unless growth has also stopped
 - b Distribution of fat is not significant except possibly in Cushing's syndrome

C HEIGHT AND EXTREMITIES

- 1 Stature
 - a Measure without shoes
 - b Check at same time of day
 - (1) Greater height is found in morning

- (2) Afternoon height may decrease by $\frac{1}{2}$ in if individual has been standing all day

- (3) A tall person shows a greater difference in morning and afternoon heights and/or with length of time in bed

- c Record height at full inspiration and deep expiration

- (1) From $\frac{1}{4}$ to $\frac{1}{2}$ in difference may be noted

- (2) Repeat observation for confirmation

- d Heightmeter with a rigid horizontal and sliding arm is preferred for measurements

- e Last growth rate may be estimated by inspection of school records

- f Factors altering measurement

- (1) Decrease—weight loss

- (2) Increase

- (a) Very erect posture

- (b) Deep inspiration

- (c) Bed rest

2 Span

- a Distance between tips of middle fingers with arms outstretched horizontally

- b An abnormal increase is not evident until after age of 12

3 Lower extremities are measured from the top of symphysis pubis to floor

4 Feet and hands

- a Growth is based on measurements of first and fifth metacarpal or metatarsal bones

- b In boys—estimations are of no practical importance

- c In girls—these bones stop growing at

- (1) Age 15, if menarche occurs before 12 years

- (2) Age 16 or 17 if menarche starts after 13 years

5 Height age—find age on 50 percentile curve (see Charts 5, 8 or 9) to which observed height of subject corresponds

6 Final height (see Charts 4 7)

- a Short remain short

- b Tall stay tall

- c Estimation from Burgess charts (see Charts 145 and 146) but is modified by age of pubescence

- 3 In most instances, hypogonitalism is apparent and not real due to excessive fat (see Figs 13 and 14)
- 4 Hypogonitalism of pituitary dwarfs is not disproportionate to somatic development and therefore is not true hypogonitalism (see 3 \IV)
- 5 True external hypogonitalism may be present
 - a From birth
 - b In prepuberal eunuchoidism, but is not often ascertained until after 13 to 15 years
- 6 Transient external hypogonitalism
 - a In some boys, growth and skeletal maturation may exceed genital development at or beyond the usual age of pubescence
 - b Until genital development begins, a transient hypogonitalism may exist

D DIFFERENTIAL DIAGNOSIS

1 Resume of normal data

- a Mental
 - (1) Age
 - (2) Responsiveness
- b Growth rate, as shown by school records
- c Height
 - (1) Above average is common
 - (2) Trend in familial heights should be studied
- d Signs of early breast development in both sexes
 - a Penis may be hidden in excess fat so that actual proportions are not evident
- f Testes
 - (1) Consistency—firm
 - (2) Size for age—up to 11 years very slight growth may take place therefore of little value in diagnosis
- g Serum phosphorus (inorganic fasting)—above 4.5 mg % until 12 or 14 years
- h Urinary FSH—greater than 6 m u /24 hrs
 - i Sella turcica
 - j Bone age—within 12 months of chronologic age by Todd's standards (see Fig 19)

- 2 Delayed pubescence (see Fig 12)
 - a Introduction—this can be rightly termed an endocrine disorder in point of time, just as sexual precocity is considered abnormal
 - b Mental age—variable
 - c Obesity—common
 - d Growth
 - (1) Rate continues normally
 - (2) Height may often be above average
 - (3) Span is increased, producing eunuchoid appearance with recovery at ages of 16 to 20 years (transient eunuchoidism)
 - (4) Theoretically, these findings may be due to delayed secretion of luteinizing hormone (LH)
 - e Breasts—may be slightly enlarged in both sexes
 - f Secondary sexual characteristics—delayed in male and female
 - g Testes
 - (1) Consistency—firm
 - (2) Size
 - (a) Normal prepubescent
 - (b) Increases (also penis) over 6 to 12 month period of observation
 - (3) Biopsy—normal but retarded development
 - h Menses—absent
 - i Serum phosphorus (inorganic fasting)—above 4.5 mg %
 - j Urinary hormone assays
 - (1) FSH
 - (a) Normal
 - (b) Increased rarely
 - (2) 17 ketosteroids—low for age
 - k Sella turcica—normal
 - l Bone age
 - (1) Normal
 - (2) Decreased
 - m Chorionic gonadotropin given to males increases
 - (1) 17 ketosteroid excretion
 - (2) Nitrogen retention
- 3 Selective gonadotropic deficiency may lead to eunuchoidism
 - a Early
 - (1) Weight—may be increased
 - (2) Height—slightly increased

E DENTAL AGE (see Tables 1 and 2)

- 1 Determined by
 - a Number of teeth
 - b Roentgen films for development of 6 12 and 18 year-old molars
- 2 Comments
 - a Retention of deciduous teeth may not indicate actual dental age
 - b Progress of secondary teeth as shown by roentgenograms is a better index

F SEXUAL DEVELOPMENT

- 1 Boys (see Table 4)
 - a Breasts may enlarge at pubescence for a short period
 - b Penis
 - (1) Erections may occur
 - (a) At any age
 - (b) In definite eunuchoids
 - (2) Measurement is of little importance before 11 or 12 years
 - (3) It is buried under fat in many
 - (4) Increase in size precedes growth of pubic hair
- c Testes
 - (1) Size
 - (a) Measure
 - [1] Length
 - [2] Width
 - [3] Thickness
 - (b) Little or no change before advent of pubescence
 - (2) Volume may be estimated by use of models (see Fig 15)
 - (3) Biopsy (see Figs 3 7)
- 2 Girls (Figs 3 4 5 6 7)
 - a Pubic hair precedes menarche
 - b Slight breast development appears before pubic hair growth
- 3 In both sexes pubic hair grows before the axillary hair, but the reverse is possible¹⁸

G EVALUATION OF VARIABLES

- 1 By summarizing the different ages and behavior patterns⁹ in normal school children including psychometric determinations an over all estimate (organismic age¹⁷) of a 10 year old child's capacity for physical and mental development is said to have prognostic significance as judged by his performances and evaluation again at 18 years of age

- 2 Perhaps too much emphasis should not be placed on these surveys in individual cases as regards prediction of mental achievement
- 3 Exceptionally bright children may approach the mean at maturity, while somewhat retarded children may advance⁵
- 4 A similar assessment is also undoubtedly applicable to endocrine cases

VI VARIATIONS OF NORMAL PUBESCENCE

A ABNORMALITIES USUALLY ATTRACTING ATTENTION

- 1 Obesity
- 2 Small genitalia

B ADIPOSEGENITAL DYSTROPHY—Frohlich's syndrome (see 3)

- 1 Obesity and small genitalia are frequently so labeled
- 2 The term was originally coined by Bartels¹ to describe a case of retarded growth and sexual development with obesity which was not different in any way from Frohlich's syndrome
- 3 The term should be restricted to this usage
- 4 Fat boys at pubescence with undeveloped genitalia are not deficient in pituitary follicle stimulating hormone (FSH)¹⁻¹⁰ but rather may be temporarily deficient in luteinizing hormone (LH) (see Figs 8 11)
- 5 Until sufficient stimulation of the gonads takes place no increase in size of testes or penis may occur
- 6 If height age or growth rate is normal and if testes show form even though of prepubescent size puberty will follow in all probability
- 7 For causes of obesity see 97 II

C EXTERNAL HYPOGENITALISM¹

- 1 This term should be employed to denote a disproportionate smallness of penis and testis in relation to general somatic development which is usually indicated by height age
- 2 Prepubescent size of genitalia may remain constant until beginning of pubescence

(2) Dosage intramuscular—1,000 to 3,000 units per week for 2 to 4 months

(3) Result—initiation of pubescence if testes are responsive

b Testosterone for males

(1) Indications

(a) Same as for chorionic gonadotropin

(b) Primary testicular disease especially (see 47 XVI A, B 1)

(2) Dosage

(a) Methyltestosterone, oral—10 to 20 mg daily for 2 to 6 months

(b) Testosterone propionate, intramuscular—10 to 20 mg per week for 2 to 6 months

(3) Results

(a) True pubescence initiated in some

(b) Substitutional development of penis and secondary sex characteristics

c Estrogens for females

(1) Indication — delayed pubescence of any type after 14 years of age

(2) Dosage stilbestrol or other estrogen preparations, oral—0.1 to 0.3 mg daily for 2 to 4 months or longer

(3) Results

(a) True menarche may follow

(b) Substitutional development of secondary sex characteristics, including uterus and external genitalia

F PROGNOSIS

1 Generally favorable even without therapy

2 Nonresponsive cases require further studies to determine outcome

REFERENCES

- 1 Bartels M Ueber die Beziehungen von Veran-
derungen der Hypophysengegend zu Miss-
wachstum und Genitalstörungen (Dystrophia
adiposogenitalis) München med Wchnschr
4 201 202 (Jan) 1908
- 2 Burgess M A The construction of two height
charts J Am Statistical Assn 32 290 310
(June) 1947
- 3 Caffey J Pediatric X-ray Diagnosis Chicago
Year Book Publishers Inc 1945 reprint 1946
pp 16 17
- 4 Cattell P Preliminary report on measurement
of ossification of hand and wrist Human Biol
6 454 471 (Sept.) 1934
- 5 Dearborn W F and Rothney J W Predict-
ing the Child's Development Cambridge Sci
Art Publishers 1941
- 6 Ellis R W B Growth and physical perform-
ance of children in relation to maturity Proc
Royal Soc Med 41 343 348 (Feb.) 1948
- 7 Gesell Arnold How a Baby Grows A Story in
Pictures New York Harper 1945 p 83
- 8 Gesell Arnold Pediatric diagnosis and supervi-
sion of child development J Omaha Mid West
Clin Soc 8 74 78 (Aug.) 1947
- 9 Greulich W W Dorfman R I Catchpole
H H Solomon C I and Culotta C S Soma-
tic and Endocrine Studies of Puberal and
Adolescent Boys Monographs of the Society for
Research in Child Development Vol VII
Washington D C National Research Council
1942 pp 1 22
- 10 Hare H F Personal communication
- 11 Hollingsworth L A S The Psychology of the
Adolescent New York Longmans 1928 p 9
- 12 Hurthall L M Hypogonadism during the
usual time of puberty JAMA 136 12 19
(Jan) 1948
- 13 Leonard D W Revised Ossification Index
for the detection of endocrine disorders in
childhood Radiology 56 716 720 (Dec.) 1946
- 14 Lasser H Testosterone ointment therapy in 6
month old baby with severe genital retarda-
tion J Clin Endocrinol 3 613 614 (Nov.)
1943
- 15 McCullagh E P and Kline I T Absence of
pituitary failure in fat boys with testicular de-
ficiency Cleveland Clin Quart 13 10 18 (Jan.)
1946
- 16 McCullagh E P Testicular dysfunction Bull
New York Acad Med 24 341 363 (June) 1948
- 17 Olsen W C and Hughes B O in Child Be-
havior and Development by R G Barker
J S Kounin and H F Wright New York
McGraw Hill 1943 pp 199 208
- 18 Priesel R and Wagner R Gesetzmässigkeiten
im Auftreten der extragenitalen sekundären
Geschlechtsmerkmale bei Mädchen (Abt. 2)
Ztschr b d ges Anat 15 333 352 (July) 1930
- 19 Schonfeld W A Management of male pubes-
cence JAMA 121 177 182 (Jan.) 1943
- 20 Schour I and Massler M Development of the
Human Dentition Chicago Chart published by
American Dental Assoc 1941
- 21 Shuttleworth F K Sexual Maturation and the
Skeletal Growth of Girls Age Six to Nineteen
Society for Research in Child Development
Washington D C National Research Council
Vol 3 No 5 Serial III 1938 pp 1 16
- 22 Ibid pp 17 20
- 23 Talbot N H and Sobel H H Endocrine and
Other Factors Determining Growth of Children
Advances in Pediatrics Vol II New York In-
terscience Publishers 1947 pp 238 297
- 24 Todd T W Atlas of Skeletal Maturation St
Louis Mosby 1937

- (3) Span—normal
- (4) Breast development—absent in females
- (5) Testes and penis—may be small for age
- (6) Serum phosphorus (inorganic fasting) — normal above 4.5 mg %
- (7) Urinary FSH — absent less than 10 m u /24 hrs
- (8) Bone age—retarded a little
- b Late
 - (1) Weight—may be increased
 - (2) Height—often above normal
 - (3) Span—greater than height
 - (4) Pubic or axillary hair
 - (a) Absent
 - (b) Scant
 - (5) Secondary sexual characteristics—absent
 - (6) Urinary hormone assays
 - (a) FSH—absent
 - (b) 17 ketosteroids—low
 - (7) Bone age—retarded
- c Comment—differentiation of this condition from delayed pubescence before the age of 15 is most difficult
- 4 Primary disease of gonads leading to eunuchoidism
 - a Early
 - (1) Weight—may be increased
 - (2) Height—slightly increased but may be subnormal
 - (3) Span—normal
 - (4) Breast development—absent
 - (5) Testes
 - (a) Consistency—soft or mushy
 - (b) Size—minuscule or absent
 - (c) Biopsy—evidence of destructive disease
 - (6) Bone age—retarded somewhat
 - b Late
 - (1) Weight—may be increased
 - (2) Height—well above average
 - (3) Span—greater than height
 - (4) Axillary and pubic hair—scant and some facial hair is possibly present
 - (5) Breast development—delayed
 - (6) External genitalia—retarded
 - (7) Testicular biopsy—as above

- (8) Urinary hormone assays
 - (a) FSH—positive
 - (b) 17 ketosteroids—variable
- (9) Bone age—retarded

E TREATMENT

1 General

- a Obesity when present should be first point of attack
- b Glutular therapy should be postponed until 14 or 15 years of age pending observations which indicate beginning and progressing pubescence unless primary testicular disease is proved
- c True hypogonadism as defined above is an indication for therapy

2 External hypogonadism in

a Infancy¹⁴

- (1) Indications—see above
- (2) Methyltestosterone injection—1 to 2 mg daily
- (3) Result—development may occur

b Pubescence

- (1) Indications—see delayed pubescence
- (2) Methyltestosterone oral—5 to 20 mg daily
- (3) Result—growth of genitalia may be observed

3 Hormonal

a Chorionic gonadotropin for males

(1) Indications

- (a) True external hypogonadism—as a trial
- (b) Delayed pubescence

- [1] If no progress in size of genitalia by age 14 under observation or earlier for psychological reasons
- [2] After exclusion of primary testicular disease
- [3] To differentiate after age of 14 between hypogonadotropic (primary testicular disease) and hypogonadotropic (secondary testicular failure) deficiency

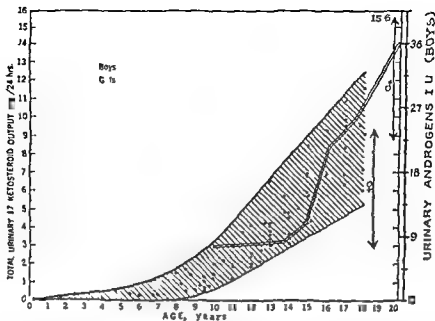


CHART 3 17 KETOSTEROIDS Total urinary 17 ketosteroids (including estrogens) in boys and girls along with biologically assayed androgens (double line) in boys up to 20 years of age. The average range of 17 keto steroids for males and females is shown in vertical lines at the right. Note that males have greater quantities. The wide variation in individual cases during pubescence and puberty demonstrates the limited value of these determinations. The degree and the progression of genital development provide a more reliable index than estimation of these studies (Greulich W W, Dorfman R I, Catchpole H C, Solomon C I and Culotta C S. Somatic and Endocrine Studies of Pubertal and Adolescent Boys. Washington D C: Child Development Publications of the Society for Research in Child Development, National Research Council pp 25-35. Levine S Z, Butler A M, Holt L E Jr and Welch T A. Advances in Pediatrics Vol II. New York and London: Interscience Publishers Inc p 272).

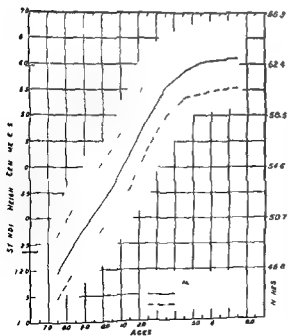


CHART 4 GROWTH AND MENARCHE Growth trends in average height of girls with same age of onset of menarche (13 to 13.5 years). The groups are divided into the tallest, the middle and the shortest cases. This chart shows that based on averages the final height in 2 girls with menarche at the same age probably can be predicted according to their height at menarche (Shuttleworth F K. Sexual Maturation and the Physical Growth of Girls Age 6 to 19. Child Development Publications of the Society for Research in Child Development, National Research Council, Washington D C p 39).

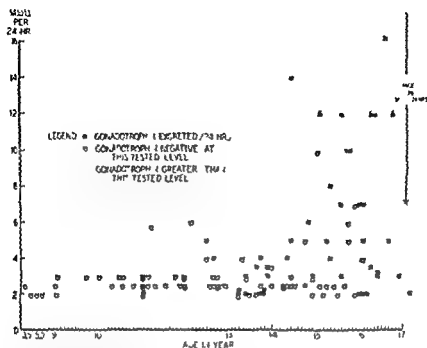
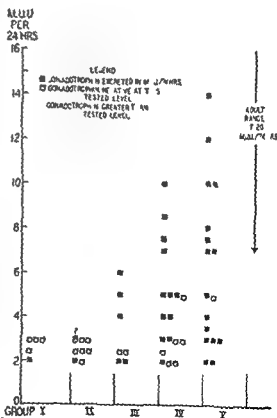


CHART 1 NORMAL DEVELOPMENT Urinary excretion of gonadotropin (FSH) in normal boys according to chronologic age (9 to 17 years of age) Note wide variations and the rather large number of cases that have very little output between 13 and 16 years. It is obvious that no prognostic significance can be attached to such determinations. Muu = mouse urine units (Greulich W W Dorfman R I Catchpole H R Solomon C I and Culotta C S Somatic and Endocrine Studies of Pubertal and Adolescent Boys Washington D C Child Development Publications of the Society for Research in Child Development National Research Council p 54)

CHART 2 URINARY EXCRETION OF GONADOTROPIN ACCORDING TO DEVELOPMENTAL GROUP STATUS IN NORMAL BOYS A better correlation exists here showing that the physical status is as good an index of development as the measurements of gonadotropin (FSH). Muu = mouse urine units (Greulich W W Dorfman R I Catchpole H R Solomon C I and Culotta C S Somatic and Endocrine Studies of Pubertal and Adolescent Boys Washington D C Child Development Publications of the Society for Research in Child Development National Research Council p 55)



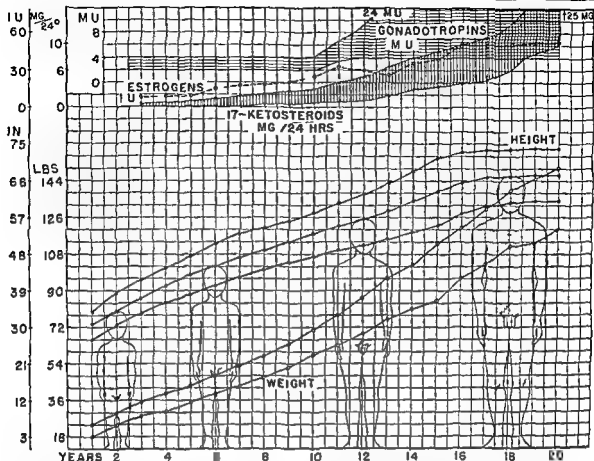


CHART 8 NORMAL DEVELOPMENT IN THE MALE Body proportions and secondary sex characteristics are plotted with weight and height curves Average height 50 percentile curve is between 99 (top) and 1 (bottom) percentile lines (Burgess) Urinary hormone assays are indicated on top of the graph Gonadotropin and 17 ketosteroid levels exceed chart space

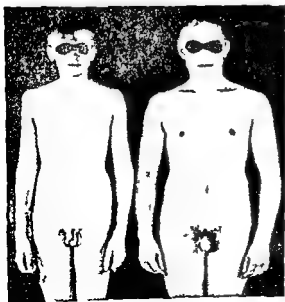


FIG 1 VARIATION IN NORMAL DEVELOPMENT Boys of same chronologic age (14.2 years) but with a somatic age of 12.4 years on the left and 16.8 years on the right Both boys normal Note difference in height

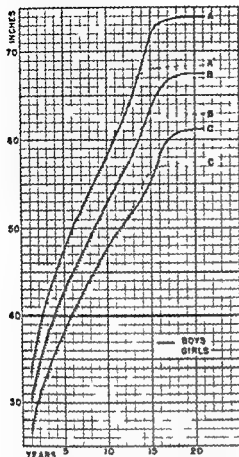


CHART 5 HEIGHT CHART This graph shows the average curves (B and B') for boys and girls and the extremes (A and A') which are the 99 percentile curves meaning that 99% of children are below these measurements while C and C' are the one percentile curves. Height age may be calculated from the curves by finding measured height of subject on curve B for boys and B' for girls and reading off the figure at the bottom of the chart (Burgess M. A. The construction of two height charts J. of Am. Statistical Assn 32 290)

CHART 6 NORMAL DEVELOPMENT Height and growth trends in earliest menarcheal Group A (before 11½ years) and in latest menarcheal Group H (14 to 15 years). The cross hatching of each curve represents the standard deviation in each group. Note that younger maturing girls on the average reach an earlier plateau (Shuttleworth F. K. Sexual Maturation and the Physical Growth of Girls Age 6 to 19 Child Development Publications of the Society for Research in Child Development National Research Council Washington D. C. p 53)

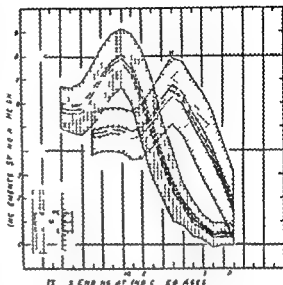
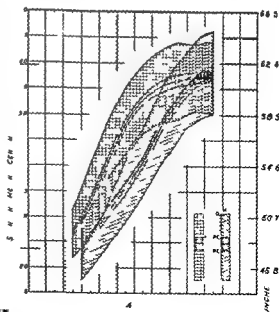


CHART 7 GROWTH AND MENARCHE Average annual increments in height of girls having early (A) and late (H) menarche. It will be noted that the pubertal spurt in growth is delayed in cases with late menarche. Thus prediction of final height can be estimated only from time of menarche or shortly thereafter. The fall in annual increment probably corresponds with decrease in growth hormone secretion (Shuttleworth F. K. Sexual Maturation and the Physical Growth of Girls Age 6 to 19 Child Development Publications of the Society for Research in Child Development National Research Council Washington D. C. p 56)



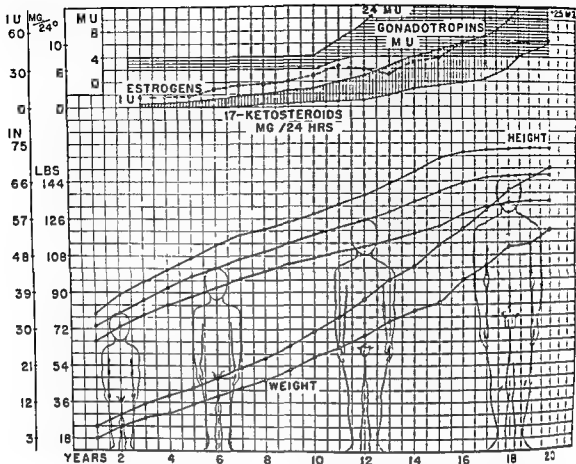


CHART 8 NORMAL DEVELOPMENT IN THE MALE Body proportions and secondary sex characteristics are plotted with weight and height curves. Average height 50 percentile curve is between 99 (top) and 1 (bottom) percentile lines (Burgess). Urinary hormone assays are indicated on top of the graph. Gonadotropin and 17 ketosteroid levels exceed chart scale.

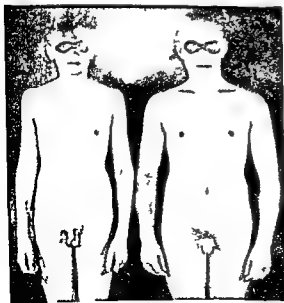


FIG 1 VARIATION IN NORMAL DEVELOPMENT Boys of same chronologic age (14.2 years) but with a somatic age of 12.4 years on the left and 16.8 years on the right. Both boys normal. Note difference in height.

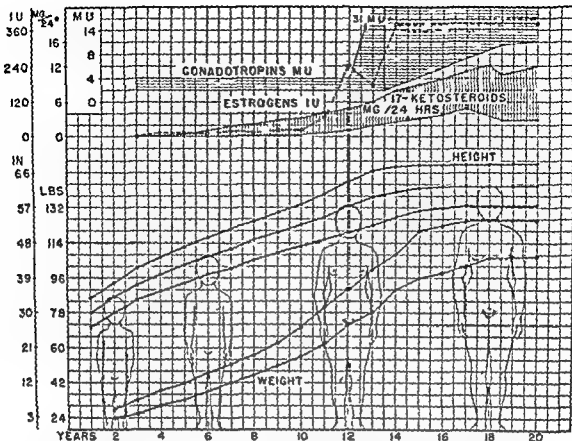


CHART 9 NORMAL DEVELOPMENT IN THE FEMALE Body proportions and secondary sexual development are plotted with weight and height curves Average height 50 percentile curve is between the 99 (top) and 1 (bottom) percentile lines (Burgess) Urinary hormone findings are included Gonadotropin levels exceed chart space After menarche the estrogen levels vary with the menstrual cycle

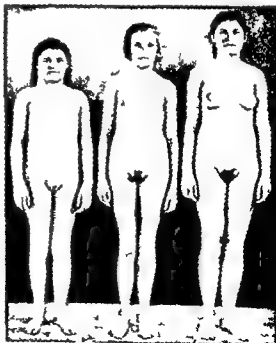


FIG 2 VARIATIONS IN HEIGHT AND SECONDARY SEX DEVELOPMENT Normal girls from 13 to 14 years of age (Priesel R and Wagner R Gesetzmassigkeiten im Auftreten der extragenitalen sekundaren Geschlechtsmerkmale bei Madchen Zeitschrift fur Konstitutionslehre 15 333)

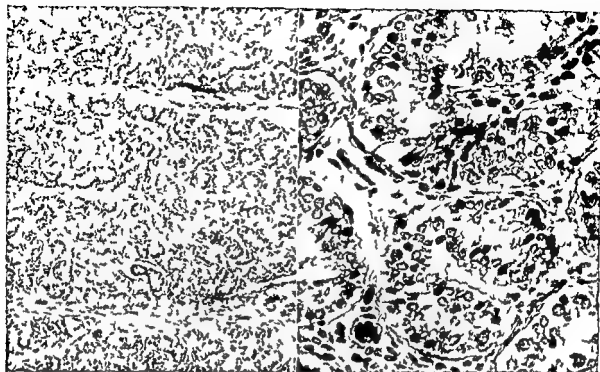


FIG 3 SEVEN YEAR OLD TESTIS—NORMAL Tubules close together No Leydig cells Tubular cells not clearly differentiated probably mostly Sertoli cells few cells suggest early spermatogonia Postmortem specimen [(left) x 90, (right) x 370]

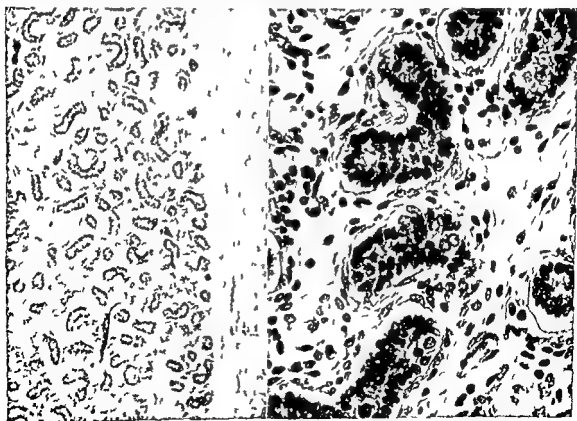


FIG 4 SEVEN YEAR OLD TESTIS—CRANIOPHARYNGIOMA Tubules widely spaced Spermatogonia clearly present Specimen illustrates variation at this age In this case spermatogonia would suggest greater maturity than in a 7 year old normal Postmortem specimen [(left) x 78 (right) x 380]

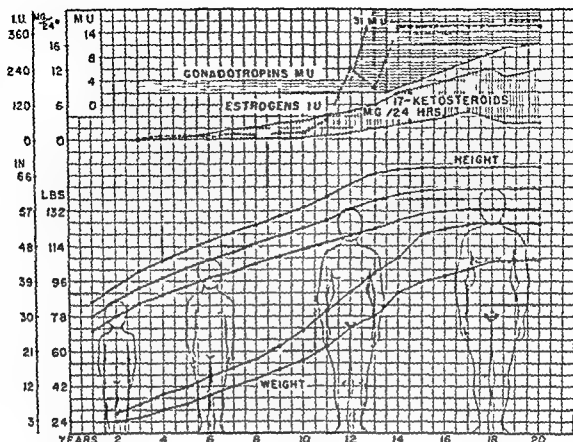


CHART 9 NORMAL DEVELOPMENT IN THE FEMALE Body proportions and secondary sexual development are plotted with weight and height curves. Average height 50 percentile curve is between the 99 (top) and 1 (bottom) percentile lines (Burgess). Urinary hormone findings are included. Gonadotropin levels exceed chart space. After menarche the estrogen levels vary with the menstrual cycle.

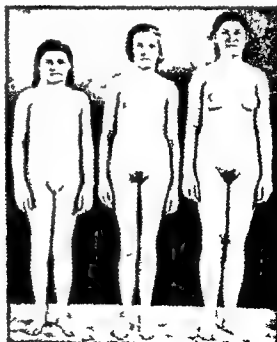


FIG 2 VARIATIONS IN HEIGHT AND SECONDARY SEX DEVELOPMENT Normal girls from 13 to 14 years of age (Priesel R and Wagner R. Gesetzmassigkeiten im Auftreten der extragenitalen sekundaren Geschlechtsmerkmale bei Mädchen. Zeitschrift fur Konstitutionslehre 15 333).

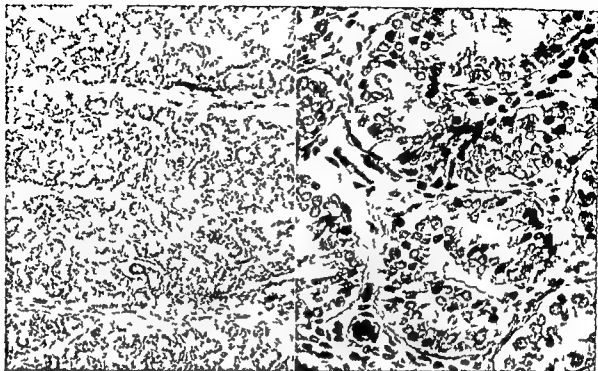


FIG 3 SEVEN YEAR OLD TESTIS—NORMAL Tubules close together No Leydig cells Tubular cells not clearly differentiated probably mostly Sertoli cells, few cells suggest early spermatogonia Postmortem specimen [(left) x 90, (right) x 370]

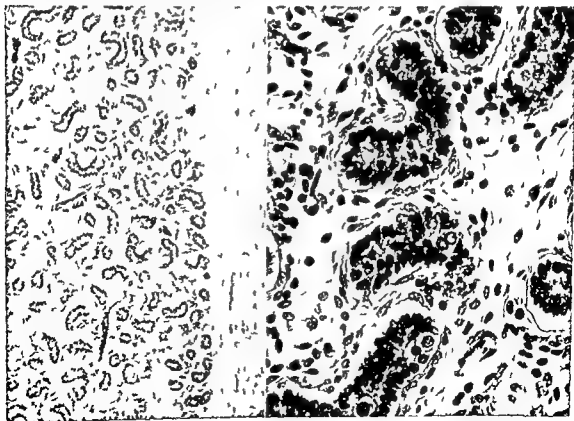


FIG 4 SEVEN YEAR OLD TESTIS—CRANIOPHARYNGIOMA Tubules widely spaced Spermatogonia clearly present Specimen illustrates variation at this age In this case spermatogonia would suggest greater maturity than in a 7 year old normal Postmortem specimen [(left) x 78 (right) x 380]



FIG 5 (Top, left) THIRTEEN YEAR-OLD TESTIS—NORMAL Tubules close together Greater maturation than at 7 years Evidence of Leydig cell formation scanty Post mortem specimen (x 27)

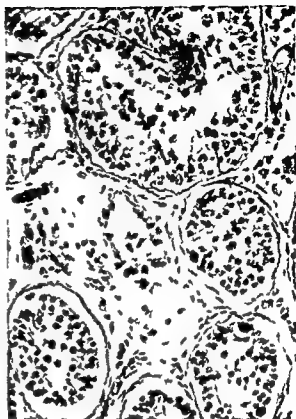
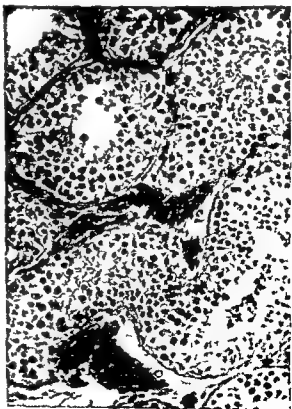


FIG 6 (Top right) NINETEEN YEAR OLD TESTIS—NORMAL Very little interstitial connective tissue Spermatocytes and spermatozoa present Leydig cells evident but not prominent Postmortem specimen (x 175)

FIG 7 (Bottom) ADULT TESTIS (See also Fig 288) Age 57 All phases of spermatogenesis present Cluster of Leydig cells in center Some thickening of basement membrane which is not infrequent at this age Castration specimen (x 265) (Drs Vernon P Dick and William A Meissner)



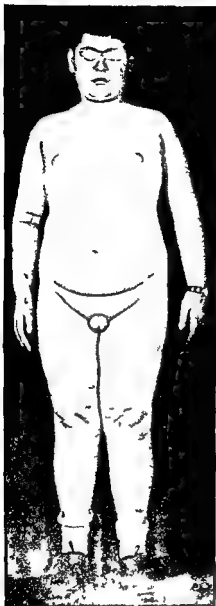


FIG 8 MODERATE OBESITY AND APPARENT EXTERNAL HYPOGENITALISM IN A PUBESCENT BOY Age 12 years Height 61 in Height age 14 years Penis hidden in pubic fat Volume of each testis approximately 4 cc The size of the testes indicates pubescence is under way The height precludes hypopituitarism This case cannot be classified as hypogenitalism because the genitalia are normal in relation to somatic development The prominent breasts are an indication of pubescence

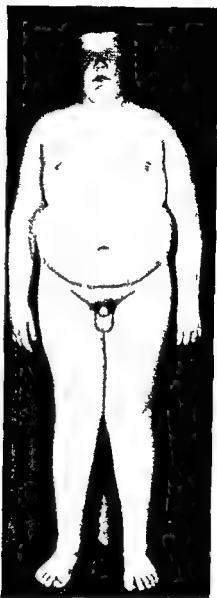


FIG 9 OBESITY IN PUBESCENT BOY Note hippy distribution of fat and prominence of breasts It is often impossible to determine whether breast size is due to obesity alone or to pubescence The genital development is normal for age in every way No endocrine disorder This is the usual outcome of fat boys with seemingly small genitals over which some parents are greatly concerned

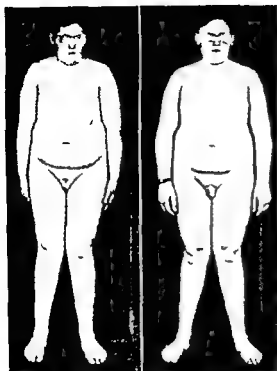


FIG 10 HYPOGENITALISM RESPONDING TO TESTOSTERONE (Left) Fourteen year old boy after 1 year of unsuccessful therapy elsewhere with chorionic hormone—1 000 units weekly (question of sufficient quantity) Weight 170 lbs Height 60½ in Height age 14 years Bone age 14 years Urinary follicle stimulating hormone (FSH) test was negative on 2 occasions (less than 80 m u) 17 ketosteroids 3.4 mg in 24 hrs The volume of each testis was less than 2 cc For 3 months unsuccessful attempts were made to diet for weight reduction Meanwhile there was growth of ¾ in (Right) After 25 days of methyltestosterone 30 mg per day volume of the testis increased to 5 cc Dose reduced to 10 mg daily for 3 months then discontinued Right testis re-entered canal thereafter (Hurxthal L M Hypogonadism during the usual time of puberty J A M A 136 12)



FIG 11 CONDITION OF BOY SHOWN IN FIGURE 10 TWO YEARS LATER WITH NO TREATMENT Height 64 in Height age 15½ years Pubic hair growing Penis length normal Volume of left testis about 18 cc Right testis in canal Erections Progress satisfactory except for weight Pinkish striae developed after renewed and partially successful attempts at weight reduction Both testes in scrotum at 18 with normal secondary sexual characteristics



FIG 12 DELAYED PUBERTY WITH NORMAL OUTCOME *Family history* Father 69 in Mother 62 in One brother age 15 years height 57 in Another brother age 16 height 58 in *History of present illness* Normal libido Frequent erections Bed wetter until 16 years Good health *Physical examination* Age 17 years Weight 110 lbs Height 57 in Height age 12 years Bone age 14½ years No axillary hair Few pubic hairs Volume of testis 5 to 6 cc *Laboratory findings* Urine and blood normal Plasma cholesterol 175 mg % Urinary hormone assays FSH negative (unconcentrated) and 17 ketosteroids 1 mg/24 hrs *Comment* No treatment recommended He served 3 years in the Army having been inducted at age of 18 years Final height at 21 years was 64 in No explanation was found for this delay in puberty

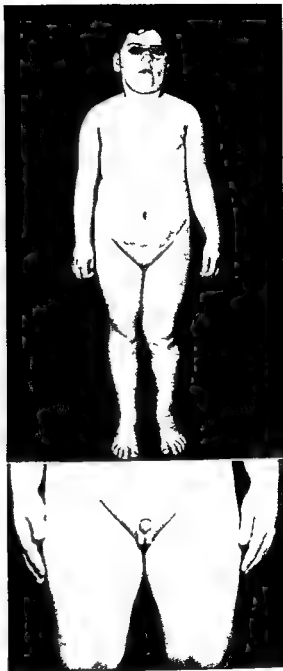


FIG 13 APPARENT HYPOGENITALISM (Top) Appearance when standing with legs together (Bottom) Close up view taken at same time legs apart Testis volume 2 cc normal for his age of 6



FIG 14 PREPUBESCENT BOY WITH APPARENT HYPOGENITALISM (*Left*) The penis looks small because of massive obesity (160 lbs) The testes were in the lower inguinal canal but had been seen in scrotum by parent estimated to be 2 cc in volume Age 11 years Height 61½ in Height age 14 years Bone age 14 years Administration of 10 000 units of chorionic hormone was followed by slight further descent of testes and progression in size thereafter Follicle stimulating hormone (FSH) test was positive estimated at more than 30 and less than 80 m u per liter before therapy Urinary estrogens—2 plus (*Right*) Four years later Weight 209 lbs Height 68½ in Height age 18 years Testis 10 cc volume Penis normal although largely buried in mons Periodic attempts at dieting unsuccessful The effect of chorionic gonadotropin was indefinite in this case although it may have initiated testicular growth (Hurxthal L M Hypogenitalism during the usual time of puberty JAMA 136 12)



FIG 15 MODELS USED FOR ESTIMATION OF TESTICULAR SIZE The smallest represents 2 cc volume which is normal until pubescence The largest volume 18 cc is usually found in a normal 18 year old boy or over The intermediate models represent growth from the beginning of pubescence until its termination (Hurxthal L M Hypogenitalism during the usual time of puberty JAMA 136 12)

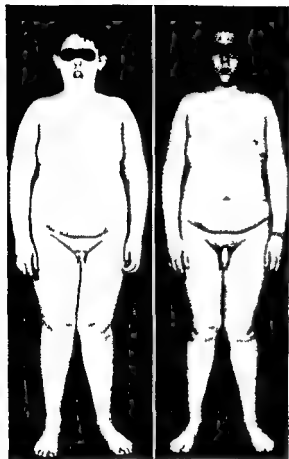


FIG 16 CRYPTORCHIDISM OBESITY AND HYPOGENITALISM IN A BOY ABOVE AVERAGE HEIGHT (See also Fig 1, and Chart 10) *Chief complaint* Obesity. *History of present illness* Overweight since the age of 3. Retarded genital development. Undescended testes noted at the age of 5. From the age of 6 chorionic gonadotropin had been administered almost continuously until the age of 8. Testosterone propionate 5 mg. was then given weekly for 1 year. (Patient has been treated elsewhere.) Testes descended. Perfectly well. *Physical examination* Age 10 Height 57½ in. Height age 12½ years Testis volume 2 cc. Photograph (left) taken at age 12. *Laboratory data* Urinary hormone assays: FSH (unconcentrated) negative and 17 ketosteroids 9.3 mg./24 hrs. *Roentgenographic findings* Bone age 12½ years. (Right) Age 13 years Weight 156 lbs Height 63½ in. Some pubic hair. Penis 3.6 in. Testis volume 10 cc. After cessation of therapy progress continued.



FIG 17 TESTICULAR BIOPSY (See also FIG 16 and CHART 10) Specimen taken at age 12 before therapy. (Left) Low power magnification. (Right) high power magnification. Seminiferous tubules—width—very small just beyond cord stage. Sertoli cells—present. Cells of spermatogenesis—spermatogonia very rare. Lumen—small filled with debris. Basement membrane—normal. Indistinct Leydig cells—none. Interstitial tissue—increased but probably normal for stage of development. Blood vessels—normal.

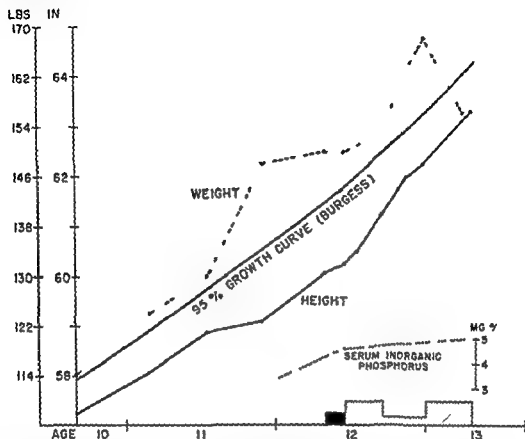


CHART 10. CRYPTORCHIDISM, APPARENT HYPOGONADISM AND OBESITY (See also Figs 16 and 1.) Patient was treated by his family physician from the age of 6 to 9 years with chonionic gonadotropin and small doses of testosterone. Treatment was discontinued 1 year before first observation. In view of the normal bone age and urinary 17 ketosteroids no therapy was advised. Fifteen months after his first observation there was a slowing down in growth and no further genital development. Testicular biopsy taken at the age of 12 was about the average for an 8 year old (see Fig 17). Fasting serum inorganic phosphorus (3.4 mg %) was low. Note gain in weight during retardation of growth. No increase in size of penis or testes for 9 more months. Then chonionic gonadotropin—4 000 units weekly—was given for 6 weeks with noticeable effect on size of testes and number of erections. With methyltestosterone 2½ to 5 mg daily there probably was an increased growth rate. Serum inorganic phosphorus levels increased concomitantly. When methyltestosterone dosage was decreased growth rate continued. Weight loss was due to more careful dieting. This case illustrates a transient decline in growth rate, cause unknown, the histology of the testes in a prepubescent boy—in whom the bone age and 17 ketosteroid output was normal in spite of absence of Leydig cells. Therapy was instituted first because of growth lag and secondly to hasten development of genitalia for psychologic reasons. No therapeutic success can be claimed for this boy except possibly as regards genital enlargement. No apparent harm results from this type of priming therapy, and often pubescence is initiated. Solid area chonionic gonadotropin—4 000 units per week. Hatched area methyltestosterone—2 and 5 mg sublingually daily.

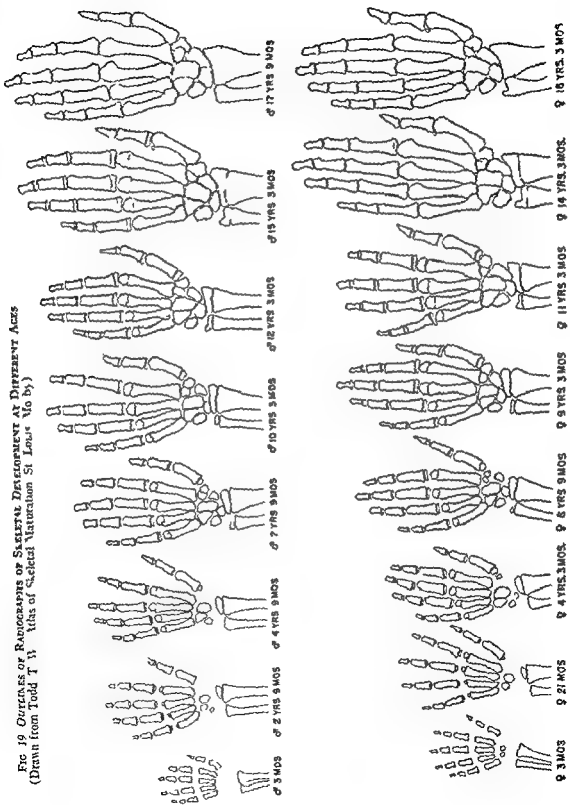


FIG 18 OSSIFICATION INDEX Diagrammatic representation of the development and latest ages (in circles) of the ossification centers in the normal. Extremes of normal ranges are listed below. The ossification index devised by Leonard may be computed when one or more centers have not appeared at the usual time in which case ossification is retarded.

BONE	EARLIEST	LATEST	MAJORITY
Capitate	Birth	6 Months	2½ Months
Hamate	Birth	7	3½
	Years	Years	Years
Radius (epiphysis)	½	2	1
Triquetrum	1	4	2¾
Lunate	2	5	4
Navicular	4	6	5
Lesser multangular	4	7	5¼
Greater multangular	4	7	5¾
Ulna (epiphysis)	5	8	6¾

(Leonard D W. Early recognition of endocrine disorders in childhood by roentgenograms of the wrist to determine the Ossification Index. Am J Roentgenol 53:55)

FIG. 19. *OUTLINES OF RADIOGRAPHS OF SKELETAL DEVELOPMENT AT DIFFERENT AGES*
 (Drawn from Todd T. 11 Atlas of Skeletal Maturation St. Louis Mo by)



CHAPTER 2

Pituitary

PRECLINICAL

Section 2 PRELIMINARY

- I HISTORY
- II ANATOMY
- III EMBRYOLOGY
- IV CONGENITAL ANOMALIES
- V HISTOLOGY
- VI FUNCTIONS
- VII CHEMISTRY
- VIII BIO ASSAY
- IX PATHOLOGY
- X CLASSIFICATIONS
- XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION
- XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION
- XIII EXAMINATION OF PATIENT
- XIV SELLA TURCICA

CLINICAL

Section

- 3 PREPUBERAL HYPOPITUITARISM
 - 4 POSTPUBERAL HYPOPITUITARISM
 - 5 SIMMONDS DISEASE
 - 6 PITUITARY MYXEDEMA
 - 7 PITUITARY ADRENAL INSUFFICIENCY
 - 8 DIABETES INSIPIDUS
 - 9 GIGANTISM
 - 10 ACROMEGALY
 - 11 CUSHING'S SYNDROME (BASOPHILISM)
 - 12 CHROMOPHOBE TUMORS
 - 13 SUMMARY OF TUMORS
-

SECTION 2

PRELIMINARY

I HISTORY

AD 130-200	Galen ⁷⁴	Pituitary discovered
1543	Vesalius ⁷⁵	This gland has an excretory function
1708	Willis ⁷⁶	Control of cerebrospinal fluid by it
1724	Santorini ⁷⁷	Anterior lobe described
1759	Haen ⁷⁸	Amenorrhea occurred with pituitary tumor
1778	Sommerring ⁷⁹	Pituitary named 'hypophysis'
1794	Frank ⁸⁰	Diabetes mellitus and diabetes insipidus differentiated
1801	Saucerotte ⁸¹	First clinical account of a case later known to be acromegaly
1838	Rathke ⁸²	Comparative anatomy and embryology of the gland described
1840	Mohr ⁸³	Obesity with invasive pituitary tumor reported
1864	Verga ⁸⁴	First autopsied acromegalic case recorded
1884	Fritsche and Klebs ⁸⁵	Enlarged pituitary in a giant
1885	Wadsworth ⁸⁶	Myxedema may be caused by a pituitary tumor
1886	Horsley ⁸⁷	Hypophysectomy successfully performed in dogs
1886	Marie ⁸⁸	Term 'acromegaly' originated
1871	Faneau de la Cour ⁸⁹	'Infantilism' is due to hypopituitarism
1887	Winkowski ⁹⁰	Pituitary enlargement found in acromegaly
1888	Rogowitsch ⁹¹	Thyroidectomy produced an increase in size of hypophysis
1891	Paultauf ⁹²	Pituitary dwarfism described
1892	Vassale and Sacchi ⁹³	Anterior lobe injury promoted polyuria
1893	Caton and Paul ⁹⁴	Acromegaly treated by cerebral surgery (unsuccessful)
1894	Tamburini ⁹⁵	Hyperactivity and hypertrophy of the pituitary causes acromegaly
1895	Oliver and Schafer ⁹⁶	Pressor action of posterior pituitary extracts discussed
1898	Comte ⁹⁷	Pregnancy produces hypophyseal enlargement
1900	Babinski ⁹⁸	Adiposogenitalis noted
1900	Benda ⁹⁹	Eosinophilic cells of pituitary are increased in acromegaly
1901	Frohlich ¹⁰⁰	Syndrome of dwarfism, delayed sexual development and pituitary tumor described
1906	Cushing ¹⁰¹	Sexual infantilism with optic atrophy observed in pituitary tumors
1906	Schlosser ¹⁰²	Successful cerebral operation performed on acromegalic patient
1908	Bartels ¹⁰³	Term adiposogenitalis coined
1908	Paulesco ¹⁰⁴	Removal of anterior lobe was fatal whereas posterior lobe produced negative results
1909	Aschner ¹⁰⁵	Anterior lobe removal accomplished successfully in dogs
1909	Bell ¹⁰⁶	Posterior pituitary extracts used in obstetrics
1909	Dale ¹⁰⁷	Oxytocic action shown in posterior pituitary extracts
1910	Crowe Cushing and Homans ¹⁰⁸	Complete hypophysectomy in dogs led to death of the animals with peculiar and characteristic symptoms (cachexia hypophyseopriva)
1911	Hirsch ¹⁰⁹	Endonasal method introduced for surgery of pituitary tumors
1913	Goldzieher ¹¹⁰	Diabetes insipidus is due to a destructive lesion in pituitary
1914	Simmonds	Fatal cachexia caused by pituitary failure
1916	Erdheim ¹¹¹	Pituitary dwarfism ('nanosomia pituitaria') recognized
1917	Allen ¹¹²	Thyroid atrophy resulted from absence of pituitary
1918	Hofbauer ¹¹³	Eclampsia may be due to hypersecretion of posterior lobe
1921	Evans and Long ¹¹⁴	Growth promoting influence of anterior pituitary demonstrated

SECTION 2

PRELIMINARY

I HISTORY

AD 130-200	Galen ⁷⁰	Pituitary discovered
1543	Vesalius ⁷²	This gland has an excretory function
1708	Willis ⁶⁴	Control of cerebrospinal fluid by it
1724	Santorini ¹⁷	Anterior lobe described
1759	Haen ⁷³	Amenorrhea occurred with pituitary tumor
1778	Sommerring ³⁴	Pituitary named 'hypophysis'
1794	Frank ²³	Diabetes mellitus and diabetes insipidus differentiated
1801	Stuczerotte ⁴³	First clinical account of a case later known to be acromegaly
1838	Rathke ⁴⁴	Comparative anatomy and embryology of the gland described
1840	Mohr ²⁴	Obesity with invasive pituitary tumor reported
1864	Verga ⁶¹	First autopsied acromegalic case recorded
1884	Fritzsche and Klebs ⁴	Enlarged pituitary in a giant
1885	Wadsworth ²²	Myxedema may be caused by a pituitary tumor
1886	Horsley ⁴¹	Hypophysectomy successfully performed in dogs
1886	Marie ⁴	Term 'acromegaly' originated
1871	Faneau de la Cour ¹	Infantilism is due to hypopituitarism
1887	Winkowski ³⁷	Pituitary enlargement found in acromegaly
1888	Rogowitsch ⁴⁶	Thyroidectomy produced an increase in size of hypophysis
1891	Paultauf ¹¹	Pituitary dwarfism described
1892	Vassale and Sacchi ⁶⁰	Anterior lobe injury promoted polyuria
1893	Caton and Paul ⁹	Acromegaly treated by cerebral surgery (unsuccessful)
1894	Tamburinni ⁷	Hyperactivity and hypertrophy of the pituitary causes acromegaly
1895	Oliver and Schafer ³⁹	Pressor action of posterior pituitary extracts discussed
1898	Comte ¹²	Pregnancy produces hypophyseal enlargement
1900	Babinski ¹	Adiposogenitalis noted
1900	Benda ⁸	Eosinophilic cells of pituitary are increased in acromegaly
1901	Froehlich ²⁵	Syndrome of dwarfism delayed sexual development and pituitary tumor described
1906	Cushing ¹⁶	Sexual infantilism with optic atrophy observed in pituitary tumors
1906	Schlosser ⁴⁰	Successful cerebral operation performed on acromegalic patient
1908	Bartels ⁶	Term 'adiposogenitalis' coined
1908	Paulesco ⁴⁰	Removal of anterior lobe was fatal whereas posterior lobe produced negative results
1909	Aschner ³	Anterior lobe removal accomplished successfully in dogs
1909	Bell ⁷	Posterior pituitary extracts used in obstetrics
1909	Dale ¹⁷	Oxytocic action shown in posterior pituitary extracts
1910	Crowe Cushing and Homans ¹⁴	Complete hypophysectomy in dogs led to death of the animals with peculiar and characteristic symptoms (cachexia hypophyseopriva)
1911	Hirsch ⁷³	Endonasal method introduced for surgery of pituitary tumors
1913	Goldzieher ⁷⁷	Diabetes insipidus is due to a destructive lesion in pituitary
1914	Simmonds	Fatal cachexia caused by pituitary failure
1916	Erdheim ⁹	Pituitary dwarfism ('nanosomia pituitaria') recognized
1917	Allen ¹	Thyroid atrophy resulted from absence of pituitary
1918	Hofbauer ³⁰	Eclampsia may be due to hypersecretion of posterior lobe
1921	Evans and Long ¹⁸	Growth promoting influence of anterior pituitary demonstrated

SECTION 2

PRELIMINARY

I HISTORY

AD 130	200	Galen ⁷¹	Pituitary discovered
1543		Vesalius ⁷²	This gland has an excretory function
1708		Willis ⁷⁴	Control of cerebrospinal fluid by it
1724		Santorini ⁷⁷	Anterior lobe described
1759		Haen ⁷⁴	Amenorrhea occurred with pituitary tumor
1778		Sommerring ⁵⁴	Pituitary named 'hypophysis'
1794		Frank ²³	Diabetes mellitus and diabetes insipidus differentiated
1801		Saucerotte ⁴³	First clinical account of a case later known to be acromegaly
1838		Rathke ⁴¹	Comparative anatomy and embryology of the gland described
1840		Mohr ³⁸	Obesity with invasive pituitary tumor reported
1864		Verga ⁸¹	First autopsied acromegalic case recorded
1884		Fritzsche and Klebs ¹	Enlarged pituitary in a giant
1885		Wadsworth ⁶³	Myxedema may be caused by a pituitary tumor
1886		Horsley ³¹	Hypophysectomy successfully performed in dogs
1886		Marie ⁵⁴	Term 'acromegaly' originated
1871		Faneau de la Cour ¹	'Infantilism' is due to hypopituitarism
1887		Minkowski ⁷⁷	Pituitary enlargement found in acromegaly
1888		Rogowitsch ⁴¹	Thyroidectomy produced an increase in size of hypophysis
1891		Paultauf ⁴¹	Pituitary dwarfism described
1892		Vassale and Sacchi ⁶⁰	Anterior lobe injury promoted polyuria
1893		Caton and Paul ⁹	Acromegaly treated by cerebral surgery (unsuccessful)
1894		Tamburini ⁵⁷	Hyperactivity and hypertrophy of the pituitary causes acromegaly
1895		Oliver and Schafer ³⁹	Pressor action of posterior pituitary extracts discussed
1898		Comte ¹⁸	Pregnancy produces hypophyseal enlargement
1900		Babinski ⁴	Adiposogenitalis noted
1900		Benda ⁸	Eosinophilic cells of pituitary are increased in acromegaly
1901		Frohlich ³	Syndrome of dwarfism: delayed sexual development and pituitary tumor described
1906		Cushing ¹⁵	Sexual infantilism with optic atrophy observed in pituitary tumors
1906		Schlosser ⁶	Successful cerebral operation performed on acromegalic patient
1908		Bartels ⁶	Term adiposogenitalis coined
1908		Paulesco ⁴⁰	Removal of anterior lobe was fatal whereas posterior lobe produced negative results
1909		Aschner ³	Anterior lobe removal accomplished successfully in dogs
1909		Bell ⁷	Posterior pituitary extracts used in obstetrics
1909		Dale ¹⁷	Oxytocic action shown in posterior pituitary extracts
1910		Crowe, Cushing and Homans ¹⁴	Complete hypophysectomy in dogs led to death of the animals with peculiar and characteristic symptoms (cachexia hypophyseopriva)
1911		Hirsch ⁷³	Endonasal method introduced for surgery of pituitary tumors
1913		Goldzieher ²⁷	Diabetes insipidus is due to a destructive lesion in pituitary
1914		Simmonds ¹	Fatal cachexia caused by pituitary failure
1916		Erdheim ⁹	Pituitary dwarfism ('nanosomia pituitaria') recognized
1917		Allen ¹	Thyroid atrophy resulted from absence of pituitary
1918		Hofbauer ³⁰	Eclampsia may be due to hypersecretion of posterior lobe
1921		Evans and Long ¹⁹	Growth promoting influence of anterior pituitary demonstrated

1922	Philip Smith ³	Pituitary extracts or implants prevented atrophy of other endocrine glands in hypophysectomized animals
1924	Rasmussen ⁴³	Pituitary cytology analyzed
1924	Starling and Varney ³	Pituitrin action on renal flow noted
1927	Zondek and Aschheim ^{60, 67}	Gonadotropic hormone of anterior pituitary demonstrated
1928	Aschheim and Zondek ²	Pregnancy urine has gonadotropic activity ("A Z" test)
1928	Kamm et al ³³	Posterior lobe extract separated into two principles—oxytocin and vasopressin
1928	Stricker and Grueter ⁶	Lactation controlled through pituitary
1928	Uhlenhuth and Schwartzbach ⁹	Thyrotropic hormone discovered
1929	Engle ¹⁸	Castration increases pituitary gonadotropic activity
1929	Teel and Watkins ⁸	Elevation of blood inorganic phosphorus was found after administration of pituitary extracts
1930	Cole and Hart ¹⁰	Gonadotropin isolated from pregnant mare serum
1930	Houssay and Biasotti ¹	Diabetes caused by pancreatectomy in dogs could be improved by hypophysectomy
1930	Philipp ⁴²	Pregnancy urine gonadotropins are of placental origin
1930	Schapiro ⁴⁹	Cryptorchidism treated effectively with chorionic gonadotropin
1932	Riddle Bates and Dylshorn ⁴⁵	Lactogenic hormone isolated
1933	Barnes, Regan and Bueno ⁵	Thyroid hormone antagonizes antidiuretic principle of posterior pituitary
1933	Collip Anderson and Thomson ¹¹	Adrenocorticotrophic hormone identified
1933	Cushing ¹⁶	Basophilic adenoma described in relation to Cushing's disease
1934	Collip and Anderson ¹²	Antihormone theory originated
1935	Fisher, Ingram and Ranson ²²	Water balance regulated by neurohormonal mechanism
1936	McConnell ³⁸	Diabetes insipidus favorably influenced by partial thyroidectomy
1937	Young ⁶⁷	Permanent diabetes produced in puppies by injections of anterior lobe extracts
1938	Sheehan and Murdock ⁵¹	Postpartum necrosis of anterior pituitary
1940	Various workers	Follicle stimulating and luteinizing hormones purified
1943	Marx, Simpson and Evans ³⁵	Growth hormone purified

II ANATOMY

A LOCATION

- 1 A reddish gray oval body attached to the brain by a stalk (infundibulum) which is continuous with the tuber cinereum¹
- 2 Pituitary gland protected by the sella turcica, lies
 - a Behind the optic chiasma
 - b In front of the corpora mammillaria
- 3 The pituitary fossa (sella turcica) is found in the middle cranial fossa just above the body of the sphenoid bone

B PARTS (nomenclature by International Commission on Anatomic Nomenclature⁵)

- 1 Adenohypophysis (see Fig 20)
 - a Lobus glandularis
 - (1) Pars distalis
 - (2) Pars tuberalis
 - (3) Pars intermedia
 - 2 Neurohypophysis
 - a Lobus nervosus (neural lobe)
 - (1) Processus infundibuli
- } anterior lobe
} posterior lobe

- B Infundibulum (neural stalk)**
 (1) Pediculus infundibularis (stem)
 (2) Bulbus infundibularis (bulb)
 (3) Labrum infundibularis (rim) or median eminence of tuber cinereum

- c Hypophyseal stalk is made of**
 (1) Neural stalk
 (2) Sheath of portions of lobus glandularis

C WEIGHT—♂ & ♀

	Gm
1 Range	0.4 to 1.8
2 Average (males and females)	0.57
a Males	
(1) Distalis	0.3941
(2) Intermedia	0.0108 (with colloid)
(3) Nervosa	0.1206
(4) Total	0.5255
b Females	
(1) Distalis	0.4990
(2) Intermedia	0.0094 (with colloid)
(3) Nervosa	0.1101
(4) Total	0.6185
3 Variation in normal	(see 2 V D): *
a Birth	100 mg
b Early childhood	
(1) First year	150 mg
(2) Third year	300 mg
(3) Seventh year	One half of the adult size
(4) Near or at puberty	Five sixths of its maximum size
■ Adolescence	Maximum possibly not until 25
d Both sexes	
(1) With aging, increase in	
(a) Pars intermedia	
(b) Neural lobe	
(2) Tall people have larger pituitaries	
■ Males—after middle age pars distalis decreases	
f Females	
(1) Larger pituitaries than males	
(2) Pregnancy increases weight of gland	

D Size^a

- 1 Variable dimensions reported
 2 Average 10 x 13 x 6 mm

E BLOOD AND LYMPH SUPPLY¹

- 1 Arteries
 a Superior hypophyseal arteries from
 (1) Internal carotids
 (2) Circle of Willis
 b Inferior hypophyseal arteries from internal carotids
 2 Veins
 a Portal venules arise from deep and superficial plexuses of stalk
 b Termination in cavernous sinuses
 c Systemic venules do not exist
 3 Lymphatics—very little known

F NERVES¹ *

- 1 Processus infundibuli receives majority of fibers from hypothalamus (hypothalamico hypophyseal tract) which arise in
 a Supra optic nuclei
 b Tuber cinereum
 2 This tract may possibly send a few fibers to pars
 a Intermedia
 b Tuberalis
 c Distalis
 3 Carotid plexus sends unmyelinated fibers (sympathetic fibers mostly) to pars distalis
 4 Parasympathetic fibers from glossopharyngeal nerve may be found
 5 Secretory activity of pituitary may be stimulated through the cervical sympathetic tracts
 6 The exact innervation is not known definitely

III EMBRYOLOGY¹**A FORMATION OF HYPOPHYSEAL PARTS**

- 1 An evagination (Rathke's pouch) from the primitive buccal cavity (stomodaenum) forms the anterior lobe
 2 This pouch grows dorsally to meet a hollow diverticulum extending down from the floor of the third ventricle which becomes the
 a Pars nervosa of the posterior lobe
 b Pituitary stalk (infundibulum)
 3 The pars nervosa pushes into and obliterates the pouch's cavity, leaving a narrow cleft

- 4 The dorsal wall of Rathke's pouch, lying next to the posterior lobe and separated from the pars anterior by the cleft, forms the pars intermedia
- 5 The upper portion (pars tuberalis) of the pouch spreads around the pituitary stalk (infundibulum), which remains in contiguity with the third ventricle

B ORIGIN (see Fig 21)

- 1 Somatic ectoderm (primitive buccal cavity) gives rise to the pars
 - Distalis
 - Tuberalis
 - Intermedia
- 2 Neural ectoderm (floor of third ventricle) produces the
 - a Pars nervosa
 - b Pituitary stalk

C TIME OF DEVELOPMENT (in weeks)

- | | |
|----------------|---|
| 1 Five | Rathke's pouch develops |
| 2 Seven | Both primordia lie in apposition |
| 3 Eight | Anterior lobe is within the sella turcica |
| 4 Ten | Pituitary gland well formed |
| 5 Twelve | Eosinophils |
| 6 Sixteen | Basophils |
| 7 Twenty eight | Chromophobes |

IV CONGENITAL ANOMALIES

A ABSENT—Lethal cranial deformities, i.e. anencephaly

B APLASIA³

C TUMORS

- 1 Arise from embryonic cellular rests of hypophyseal (craniopharyngeal) duct, original connection of Rathke's pouch to the buccal cavity which may be called
 - a Craniopharyngioma
 - b Rathke's pouch cyst
 - c Suprasellar cyst
 - d Interpeduncular cyst
 - e Hypophyseal duct growth
- 2 Originate from other embryonic anlagen (rare)
 - a Dermoid cyst
 - b Teratoma
 - c Cholesteatoma
 - d Chordoma

D INTERPEDUNCULAR ANEURYSM

E ABERRANT TISSUE SITES

- 1 Pharynx¹
- 2 Floor of
 - Third ventricle
 - b Sella turcica between dural layers
- 3 Sphenoid bone

V HISTOLOGY^{15 19}

A ANTERIOR LOBE: (see Fig 22)

- 1 Types of cells
 - a Chromophobes (neutrophils, chief reserve or clear)
 - (1) Shape
 - (a) Small
 - (b) Rounded
 - (c) Polyhedral
 - (2) Cytoplasm
 - (a) Diffuse
 - (b) Clear
 - (c) Light staining
 - (3) Granules
 - (a) Few
 - (b) Size variable
 - (4) Cell walls—inconspicuous
 - (5) Mitochondria
 - (6) Golgi apparatus
 - b Chromophils (granular)—2 types
 - (1) Acidophils (eosinophils, oxyphils or alpha)
 - (a) Size larger than
 - [1] Chromophobes
 - [2] Basophils
 - (b) Shape
 - [1] Round
 - [2] Columnar
 - (c) Granules within cytoplasm
 - [1] Stainable with dyes acid or basic (certain ones)
 - [2] Grouped at one pole
 - [3] Scattered sometimes
 - (d) Cell walls distinct
 - (e) Mitochondria—numerous
 - (f) Golgi apparatus
 - (g) Nuclei
 - [1] Round
 - [2] Vesicular
 - [3] Chromatin scant
 - [4] Pyknotic occasionally
 - (2) Basophils (cyanophil beta)
 - (a) Granules take basic stain
 - (b) Essentially same cellular components as acidophils

2 Arrangement

- a Cells within irregular cords are surrounded by
 - (1) Basilar sinuses
 - (2) Connective tissue
- b Variable number of cells in each cord
 - (1) Chromophils—most numerous
 - (2) Acidophils—outnumber basophils
 - (3) Walls of cord—usually 1 to 2 cells in thickness
- c "Colloid" masses often present in cell cords resembling true follicles
- d Peripheral cords
 - (1) Basophils—mostly
 - (2) Chromophobes—few
- e Central cords
 - (1) Chromophobes—majority
 - (2) Acidophils—rare

3 Relationship

- a Chromophobes may become
 - (1) Acidophils
 - (2) Basophils
- b Chromophils may return to chromophobe state
- c Interchange between acidophil and basophil must take place through the chromophobe stage
- d Certain chromophobes develop only into a specific type of chromophil

4 Distribution

- a Average cellular percentages (both sexes)
 - (1) Chromophil
 - (a) Acidophilic—37 per cent
 - (b) Basophilic—11 per cent
 - (2) Chromophobes—52 per cent
- b Both sexes with aging
 - (1) Acidophils—decrease
 - (2) Chromophobes—increase
- c Males basophils are more numerous
- d Females basophilic number can increase

III INTERMEDIATE LOBE¹

- 1 A cellular remnant, often only a single layer of cells
- 2 Cells
 - a Nongranular
 - (1) Shape—polygonal
 - (2) Specific granules—absent
 - (3) Basic stain—pale
 - (4) Cilia may be present
 - (5) Follicular arrangement
 - (6) Lumen contains hyaline material

b Basophils

- (1) Smaller than those of anterior lobe
- (2) Cellular prolongation into neural lobe

C POSTERIOR LOBE²⁰

1 Cells

- a Pituitocytes (neuroglia)
 - (1) Shape
 - (a) Fusiform
 - (b) Irregular
 - (2) Granules
 - (a) Present
 - (b) Absent
 - (3) Processes
 - (a) Long
 - (b) Branching
 - (4) Nuclei
 - (a) Distinct
 - (b) Granules of fine chromatin
- b Basophils (probably originate from intermediate lobe)
 - (1) Size
 - (a) Small
 - (b) Large
 - (2) Increase with age
- 2 Hyaline bodies ("Herring bodies")
- 3 Connective tissue
- 4 Plexus of unmyelinated nerve fibers

D CONDITIONS WHICH ALTER THE PITUITARY CELLS (see 2 IV B)

1 Castration—physiologic or surgical (male or female)

a General¹⁻³ 11 1 11 15-19

- (1) Acidophils¹⁻³ 4 13 35 55
 - (a) These cells decrease slightly in
 - [1] Number
 - [2] Size
 - [3] Staining capacity
 - (b) Regress toward chromophobe state
- (2) Basophils
 - (a) These increase in
 - [1] Size
 - [2] Number
 - (b) Some of the basophils become vacuolated with a colloidlike material which displaces the nucleus giving the cells a "signet ring" appearance

- 4 The dorsal wall of Rathke's pouch, lying next to the posterior lobe and separated from the pars anterior by the cleft, forms the pars intermedia
- 5 The upper portion (pars tuberalis) of the pouch spreads around the pituitary stalk (infundibulum), which remains in contiguity with the third ventricle

B ORIGIN (see Fig 21)

- 1 Somatic ectoderm (primitive buccal cavity) gives rise to the pars
 - a Distalis
 - b Tuberalis
 - c Intermedia
- 2 Neural ectoderm (floor of third ventricle) produces the
 - a Pars nervosa
 - b Pituitary stalk

C TIME OF DEVELOPMENT (in weeks)

- 1 Five Rathke's pouch develops
- 2 Seven Both primordia lie in apposition
- 3 Eight Anterior lobe is within the sella turcica
- 4 Ten Pituitary gland well formed
- 5 Twelve Eosinophils
- 6 Sixteen Basophils
- 7 Twenty eight Chromophobes

IV CONGENITAL ANOMALIES

A ABSENT—Lethal cranial deformities i.e. anencephaly

B APLASIA³

C TUMORS

- 1 Arise from embryonic cellular rests of hypophyseal (cranopharyngeal) duct original connection of Rathke's pouch to the buccal cavity which may be called
 - a Cranopharyngioma
 - b Rathke's pouch cyst
 - c Suprasellar cyst
 - d Interpeduncular cyst
 - e Hypophyseal duct growth
- 2 Originate from other embryonic anlagen (rare)
 - a Dermoid cyst
 - b Teratoma
 - c Cholesteatoma
 - d Chordoma

D INTERPEDUNCULAR ANEURYSM

E ABERRANT TISSUE SITES

- 1 Pharynx¹
- 2 Floor of
 - a Third ventricle
 - b Sella turcica between dural layers
- 3 Sphenoid bone

V HISTOLOGY¹⁰

A ANTERIOR LOBE (see Fig 22)

- 1 Types of cells
 - a Chromophobes (neutrophils, chief reserve or clear)
 - (1) Shape
 - (a) Small
 - (b) Rounded
 - (c) Polyhedral
 - (2) Cytoplasm
 - (a) Diffuse
 - (b) Clear
 - (c) Light staining
 - (3) Granules
 - (a) Few
 - (b) Size variable
 - (4) Cell walls—inconspicuous
 - (5) Mitochondria
 - (6) Golgi apparatus
 - b Chromophils (granular)—2 types
 - (1) Acidophils (eosinophils oxyphils or alpha)
 - (a) Size larger than
 - [1] Chromophobes
 - [2] Basophils
 - (b) Shape
 - [1] Round
 - [2] Columnar
 - (c) Granules within cytoplasm
 - [1] Stainable with dyes acid or basic (certain ones)
 - [2] Grouped at one pole
 - [3] Scattered sometimes
 - (d) Cell walls distinct
 - (e) Mitochondria—numerous
 - (f) Golgi apparatus
 - (g) Nuclei
 - [1] Round
 - [2] Vesicular
 - [3] Chromatin scant
 - [4] Pyknotic occasionally
 - (2) Basophils (cyanophil beta)
 - (a) Granules take basic stain
 - (b) Essentially same cellular components as acidophils

2 Arrangement

- a. Cells within irregular cords are surrounded by
 - (1) Basilar sinuses
 - (2) Connective tissue
- b. Variable number of cells in each cord
 - (1) Chromophils—most numerous
 - (2) Acidophils—outnumber basophils
 - (3) Walls of cord—usually 1 to 2 cells in thickness
- c. Colloid masses often present in cell cords resembling true follicles
- d. Peripheral cords
 - (1) Basophils—mostly
 - (2) Chromophobes—few
- e. Central cords
 - (1) Chromophobes—majority
 - (2) Acidophils—rare

3 Relationship

- a. Chromophobes may become
 - (1) Acidophils
 - (2) Basophils
- b. Chromophils may return to chromophobe state
- c. Interchange between acidophil and basophil must take place through the chromophobe stage
- d. Certain chromophobes develop only into a specific type of chromophil

4 Distribution

- a. Average cellular percentages (both sexes)
 - (1) Chromophil
 - (a) Acidophilic—37 per cent
 - (b) Basophilic—11 per cent
 - (2) Chromophobes—52 per cent
- b. Both sexes with aging
 - (1) Acidophils—decrease
 - (2) Chromophobes—increase
- c. Males basophils are more numerous
- d. Females basophilic number can increase

B INTERMEDIATE LOBE²

- 1. A cellular remnant often only a single layer of cells
- 2. Cells
 - a. Nongranular
 - (1) Shape—polygonal
 - (2) Specific granules—absent
 - (3) Basic stain—pale
 - (4) Cilia may be present
 - (5) Follicular arrangement
 - (6) Lumen contains hyaline material

b. Basophils

- (1) Smaller than those of anterior lobe
- (2) Cellular prolongation into neural lobe

C POSTERIOR LOBE²⁰

1 Cells

a. Pituicytes (neuroglia)

- (1) Shape
 - (a) Fusiform
 - (b) Irregular
- (2) Granules
 - (a) Present
 - (b) Absent
- (3) Processes
 - (a) Long
 - (b) Branching
- (4) Nuclei
 - (a) Distinct
 - (b) Granules of fine chromatin

b. Basophils (probably originate from intermediate lobe)

- (1) Size
 - (a) Small
 - (b) Large
- (2) Increase with age

2 Hyaline bodies (Herring bodies)

3 Connective tissue

4 Plexus of unmyelinated nerve fibers

D CONDITIONS WHICH ALTER THE PITUITARY CELLS (see 2 IV B)

1 Castration—physiologic or surgical (male or female)

a. General^{1,2,3,11,12,14,15,16,17}

- (1) Acidophils^{1,2,3,11,12,14,15,16,17}
 - (a) These cells decrease slightly in
 - [1] Number
 - [2] Size
 - [3] Staining capacity
 - (b) Regress toward chromophobe state

(2) Basophils

- (a) These increase in
 - [1] Size
 - [2] Number
- (b) Some of the basophils become vacuolated with a colloidlike material which displaces the nucleus giving the cells a 'signet ring' appearance

(c) 'Castration' or "signet ring" cells do not develop in all species (rabbit or guinea pig)

(3) Cellular differentiation possible between (see 2 IX II 14)

(a) Castration

(b) Thyroidectomy

b Males (after middle age)^{19 1}

(1) Pituitary weight decreases

(2) Cellular content

(a) Acidophils—decrease

(b) Basophils—no significant change

(c) Chromophobes—increase

c Female climacteric^{1 19 1}

(1) Hypophyseal weight remains the same

(2) Cellular content

(a) Acidophils—decrease

(b) Basophils—*increase, then decrease*

(c) Chromophobes—*increase*

(3) Secretory (gonadotropic) activity increases

2 Pregnancy

a Pregnancy cells arise from chromophobes which may become^{6 12 18}

(1) Granulated

(2) Degranulated

b Acidophils and basophils^{4 8}

(1) Secrete very actively

(2) Degranulation of both types

(3) Golgi apparatus—hypertrophied

(4) Mitochondria—numerous

c Cellular findings indicate state of activity^{10 13 23}

(1) Acidophils increase in the following stages of pregnancy

(a) Early

(b) Full term

(c) Postpartum

(2) Basophils increase toward full term only

d Whole gland increases in^{7 9 14}

(1) Size

(2) Weight

a Role as the chief stimulator of bodily growth

b Hormonal dominance to a greater or lesser degree of other endocrine glands, through which most vital functions are controlled

II INDIVIDUAL HORMONES

1 Introduction

a Functions of the hormones are learned by

(1) Removal of the endocrine gland or glands

(2) Studies by replacement therapy

(3) Clinical observation on patients with the effects of hyposecretion or hypersecretion

(4) Production of an excessive amount by using

(a) Glandular extracts

(b) Isolated or synthetic compounds

b Dosage is important because giving the minimum may have the opposite effects of large amounts as demonstrated in various animals

c Since many preparations are not purified and because various hormones may be closely related there is obviously an overlapping in experimental results

d The species the diet and the environment of animals must be considered in evaluating the final conclusions

e The following are illustrative examples regarding the animal which may be used

(1) Normal (infantile or adult)

(2) Parabiotic

(3) Removal of the endocrine gland(s) either alone or plus another

f While deductions from animal studies may be projected into human physiology allowances always must be made for differences in species

g The criteria presented above apply to all hormones as discussed subsequently

2 List of hormones (principles factors)

a Anterior lobe

(1) Growth hormone (somatotrophic)

VI FUNCTIONS

A GLAND AS A WHOLE

1 The primary functions of the pituitary are probably its

- (2) Gonadotropic hormones (GTH)
 - (a) Follicle stimulating hormone (FSH, seminiferous tubular stimulating, STSH, prolan A, thylenkentrin, gametokinetic)
 - (b) Luteinizing hormone (LH, prolan B, metakentrin, interstitial cell stimulating ICSH)
 - (c) Luteotropic hormone
- (3) Thyrotropic hormone (TSH)
- (4) Adrenocorticotrophic hormone (corticotropic, adrenotropic ACTH)
- (5) Diabetogenic hormone
- (6) Galactins
 - (a) Lactogenic hormone (prolactin)
 - (b) Mammogen I (?)
 - (c) Mammogen II (?)
- (7) Adrenomedullotropic hormone (?)
- (8) Parathyrotropic hormone (?)
- (9) Splenotropic principle (?)
- (10) Metabolic hormones
 - (a) Carbohydrate
 - [1] Pancreatotropic factor (?)
 - [2] Contra insulin factor (?) (possibly the same as adrenocorticotropin)
 - [3] Glycotropic factor (?) (anti insulin factor)
 - [4] Glycostatic factor (?)
 - [5] Hyperglycemic factor (?)
 - [6] Insulotropic principle (?)
 - (b) Fat
 - [1] Ketogenic factor (?)
 - [2] Lipotropic factor (?)
 - (c) Protein metabolism factor (?)
 - (d) Water metabolism factor (?)
 - (e) Calcium factor (?)
- (11) Renotropic factor (?)
- (12) Hepatic and cardiac factors (?)
- (13) Hematopoietic factor (?)
- b Intermediate lobe
 - (1) Specific metabolic factor (?)
 - (2) Chromatophore stimulating factor (?) (melanophore erythrophore)
- c Posterior lobe
 - (1) Vasopressin
 - (2) Oxytocin
 - (3) Antidiuretic principle (?)
 - (4) Other factors (??)
 - (a) Lipotropic factor (?)
 - (b) Adrenalin inhibition factor (?)
 - (c) Hyperglycemic factor (?)
- 3 Growth hormone
 - a Its control is exerted directly and mainly on organism possibly the liver⁴³ and not through other endocrine glands²³
 - b Effective in animals which are¹⁰
 - (1) Hypophysectomized
 - (2) Thyroidectomized⁴¹
 - (3) Thyroidectomized and hypophysectomized
 - (4) Adrenalectomized^{1, 34}
 - (5) Castrated¹⁰
 - (6) Pancreatized
 - (7) Thymectomized⁴
 - c Protein metabolism—through anabolic action produces an increase in $\frac{9}{11} \frac{12}{1} \frac{21}{10} \frac{4}{3} \frac{31}{32}$
 - (1) Growth rate of skeleton (immature animals)
 - (2) Appetite
 - (3) Food consumption
 - (4) Body weight^{5, 31}
 - (5) Muscle glycogen^{22, 45}
 - (6) Cartilage proliferation^{3, 16, 28, 43, 44}
 - (7) Weight of³⁷
 - (a) Thymus
 - (b) Lymph glands
 - (c) Liver (variable)
 - (8) Specific dynamic action³⁸
 - d Carbohydrate metabolism
 - (1) Less conversion of protein to glucose in growing animals^{17, 21, 43}
 - (2) Initial hypoglycemia in adult rats is followed by hyperglycemic phase (anti insulin action)^{30, 40}

- (3) Diabetes has been produced in
 (a) Dogs (not puppies)^{4 5 8 48}
 (b) Cats⁶
 (c) Batrachians⁷³
- Alterations in tissue constituents
- (1) Weight gain due to ⁷
 (a) Fat decrease
 (b) Protein increase
 (c) Water increase
- (2) Liver
 (a) Decrease in¹⁴
 [1] Arginase
 [2] Ribonucleic acid
 (b) Increase in ⁸
 [1] Labile protein
 [2] Fatty infiltration⁴⁵
- (3) Thymus may have an increase in nucleic acid turnover
- f Respiratory quotient is decreased^{15 20 22 30}
- g Urinary excretion
- (1) No change in
 (a) Uric acid
 (b) Creatinine
- (2) Decrease in^{31 46}
 (a) Nitrogen^{14 5 29 46}
 (b) Phosphorus
 (c) Sulfur, probably
- (3) Calcium may be increased^{32 43 46}
- h Blood constituents
- (1) Decrease in
 (a) Nonprotein nitrogen^{18 47}
 (b) Amino acids (urea nitrogen unchanged)^{1 15 29}
- (2) Increase in
 (a) Inorganic phosphorus ⁶
 (b) Alkaline phosphatase
- 4 Gonadotropic hormones^{12 55}
- a Females (see 37 VI B 1 2)
- (1) Follicle (or seminiferous tubular) stimulating hormone—FSH
- (a) Stimulates^{1 1 4 35}
 [1] Follicular development (antrum to preovulatory stage)
 [2] Ovarian weight
 [3] Estrogen secretion for secondary sex development, but probably not sexual hair
- (b) No effect on
 [1] Interstitial tissue
 [2] Theca
- (2) Luteinizing (or interstitial cell stimulating) hormone—LH or ICSH
- (a) Stimulates
 [1] Corpus luteum formation which in turn secretes progesterone^{1 15 33} (prolactin may or may not be necessary for this effect^{7 9 11 37})
 [2] Interstitial cells
- (b) Inhibits possibly
 [1] Estrogen production and estrus
 [2] The further development of follicles
- b Males (see 45 VI B 1, 2)
- (1) Seminiferous tubular stimulating (or follicle stimulating) hormone—STSH or FSH
- (a) Stimulates^{8 19 20 23 25 31}
 [1] Seminiferous tubules
 [2] Spermatocytogenesis and spermatogenesis
 [3] Testicular weight
- (b) No effect on²²
 [1] Accessory sex organs
 [2] Leydig cells
 [3] Nitrogen excretion (rats)³⁰
- (2) Interstitial cell stimulating (or luteinizing) hormone—ICSH or LH
- (a) Stimulates⁷⁸
 [1] Interstitial Leydig cells of testes to secrete male sex hormone (testosterone) which in turn produces development of
 [a] Accessory sex organs^{8 19 20 23 31}
 [b] Seminiferous tubules
 [2] Testicular weight
- (b) Evidence for effect on adrenal cortex is not conclusive^{2 31}
- c Follicle stimulating and luteinizing hormones act synergistically (it is doubtful if FSH can be prepared without traces of LH and vice versa)

(1) Females (animals)

(a) I SH and minimal traces of

LH stimulate^{8 11 19 25}

{1} Ovarian weight

{2} Estrogen secretion^{13 15}
^{27 35}

{3} Progesterone formation

{4} Ovulation (follicles must
be in preovulatory
stage)^{1 3 5 11 17 26 27}{5} Involution of persisting
corpora lutea¹{6} Uterine growth (after
ovarian effects)(b) I SH and greater amounts
of LH (same effects may be
produced by inorganic salts
or inert proteins combined
with FSH¹⁹) cause follicu-
lar^{16 27}

{1} Luteinization

{2} Cystic degeneration

2) Males

(a) Testicular effects

{1} Enlargement¹⁶{2} Descent (possibly only
ICSH)^{11 22}{3} Spermatogenesis en-
hanced¹⁹(b) Accessory organs increase
in size, due to greater Leydig
cell secretion^{27 3 33}

(3) Males and females (animals)

(a) Specific dynamic action of
protein is not influenced
(hypophysectomized rats)²³(b) Alkaline phosphatase (rats)
is increased in epiphyses
and diaphyses²³(c) Creatinine excretion is in-
creased without affecting
creatinine²⁴(d) Cholesterol metabolism of
the adrenal cortex is de-
creased after a preliminary
rise (rats)⁴d) Luteotropic hormone^{9 10 20}(1) It may be same as lactogenic
hormone(2) Corpora luteal function main-
tained

5 Thyrotropic hormone (TSH)

a Introduction

(1) Primary action of thyrotropic
hormone (TSH) is upon thyroid
cells^{4 7 18 16-21 1 3-37}(2) In consequence there is an out-
pouring of thyroid hormone,
which accounts for most of the
physiologic changes following
injection of TSH (These are de-
scribed under hyperthyroidism,
14 VI B)(3) However, certain effects are in-
dependent of the thyroid gland,
since they may be produced in
thyroidectomized animals(4) Thyroid hormone on the other
hand, is considered to have an
inhibiting effect upon the

(a) Thyrotropic hormone

(b) Hypothalamus

b Effects of injection of TSH in nor-
mal or thyroidectomized animals(1) Exophthalmos may be produced
(also in castrated animals)^{1 2}
^{10 11 16 20 25 29 37 40 4 43}(2) Fat increased in^{10 11}

(a) Blood

(b) Liver

(c) Muscles

(d) Epithelial cells

(e) Lymph nodes

(f) Spleen

(g) Kidneys

(h) Polymorphonuclear leuko-
cytes

(i) Tissue macrophages

(j) Thyroid cytoplasm

(3) Blood acetone increased

c Other effects are related to second-
ary increase of thyroid hormone se-
cretion (see 14 VI B)^{3 8 9 1 25 17}
^{10 27 20 3 34 38 39-41 47 48 50 51}■ Adrenocorticotrophic hormone (cortico-
tropic adrenotropic ACTH)a Introduction (see 39 VI B 1 2, 106
III E)(1) The action of adrenocortico-
tropic hormone, or hormones is
to stimulate the adrenal cortices
^{15 25 32, 37 71}

- (2) Cortical secretions may in turn have an inhibitory influence on the pituitary,^{9 7-} while epinephrine may release ACTH^{46 53}
 - (3) With the purification of ACTH near at hand, accumulating evidence suggests that most if not all, of the secretions of the adrenal cortices are under control of one rather than several pituitary adrenocorticotrophic factors
 - (4) However, it is doubtful if such a conclusion is possible
 - (5) The action of ACTH and the effects produced by secondary elaboration of adrenocortical hormones are enumerated here, because they cannot be individually assigned to isolated hormonal compounds of the cortex
 - (6) Several categories of function may be used to illustrate the results of ACTH injections
- b Effects due to so called sugar ('S carbohydrate or glucocorticoid') hormones in experimental animals¹
- (1) Carbohydrate metabolism^{20 30 37 40}
 - (a) Carbohydrate utilization retarded⁵
 - (b) Glycogen deposition increased in
 - [1] Muscle^{29 38}
 - [2] Liver^{3 38 60}
 - (c) Gluconeogenesis^{5 38 39}
 - (d) Hyperglycemia^{38 60}
 - (e) Glycosuria^{29 38 60}
 - (f) Insulin resistance^{9 39 39}
 - (2) Fat metabolism—some deposition of fat⁴¹
 - (3) Protein metabolism
 - (a) Anti anabolic or excess catabolic action^{1 27}
 - (b) Negative nitrogen balance may be augmented by high protein intake^{1 6}
 - (c) Liver arginase activity increased^{19 21 23}
 - (d) Blood urea and nonprotein nitrogen increased⁴
 - (e) Specific dynamic action is not influenced (rats)⁵³
 - (4) Lymphoid tissue^{10 13 14 45 60 70}
 - (a) Dissolution of tissue in
 - [1] Thymus^{38 60}
 - [2] Lymph glands^{5 1}
 - (b) Serum globulins, beta and gamma^{9 77 79}
 - [1] Increased consequently
 - [2] Important in antibody formation
 - (c) Circulating white blood cells
 - [1] Lymphocytes decreased^{11 12 14 31 64 79 80}
 - [2] Eosinophils decreased³³
 - [3] Polymorphonuclears increased^{11 12 31 64 78 80}
 - (d) Splenin—a hormonal substance released from the spleen (?)³
 - (e) Resistance to stress increased^{44 58}
 - (5) Bleeding time may be decreased
 - (6) Circulating red blood cells are increased then eventually decreased^{11 60 78 79}
 - (7) Renal function may be impaired^{3 5 47}
 - (8) Growth retardation and decreased^{46 6 18 33 48 60}
 - (a) Chondrogenesis
 - (b) Osteogenesis
 - (c) Alkaline phosphatase (serum)⁴³
 - (d) Osteoblastic activity⁸⁴
 - (9) Endocrine glands
 - (a) Thyroid¹²
 - [1] Weight—decreased
 - [2] Hypoplasia—produced
 - (b) Adrenal cortices show depletion of
 - [1] Cholesterol^{7 60 63 74}
 - [2] Ascorbic acid⁶¹
 - (c) Testes and accessory sex organs^{6 74}
 - [1] Atrophy (normal or hypophysectomized rats)
 - [2] Prostate (ventral) increased (hypophysectomized rats)⁷⁴

(d) Pancreas

- [1] Insulin content increased (rats) to an average of 40 per cent above normal level²⁰
- [2] If removed severe protein breakdown and diabetes⁶¹

(10) Mammary glands—prolactin is aided in initiation of lactation^{70 49 46}

- c Effects due to so-called nitrogen retaining protein anabolic or "N hormone" are not clearly demonstrated with injections of ACTH, possibly because "S" hormones are dominant
- d Results due to salt regulating or mineral hormones are not proved very well in experimental animals by injections of ACTH
- e Effect of ACTH by injection in normal humans (see also 106 III E 3)
^{8 18 47 57}

(1) Comment — changes reported vary with different observers probably because of

- (a) Dosage
- (b) Purity of extract
- (c) Conditions of experiment

(2) Hematologic findings⁴⁷

- (a) Hemoglobin decreased
- (b) White blood cells^{15 70 57}
 - [1] Eosinophils decreased⁷³
 - [2] Lymphocytes decreased
 - [3] Polymorphonuclears increased

(c) Cell volume decreased

(3) Urinary excretion

- (a) No change in⁴⁷
 - [1] Gonadotropins
 - [2] Estrogens
 - [3] Pregnenolol
- (b) Decrease in^{47 64}
 - [1] Creatinine (or no change)
 - [2] Creatine
- (c) Increase in
 - [1] Sugar^{8 57}
 - [2] Total nitrogen (see 106 III E 3 f)^{8 18 9}
 - [3] Uric acid^{18 13 17 18}

[4] Potassium (but variable)^{18 47 7}

[5] Sodium (but variable)
^{18 47}

[6] Chloride (or decrease)
^{18 57}

[7] 17 ketosteroids^{18 47 81}

[8] Cortinlike substances^{18 47 81}

[9] 11 oxysteroids^{18 47}

[10] Androsterone⁴⁷

[11] Etiocholanolone⁴⁷

(4) Blood chemical analyses

(a) No change in⁴⁷

[1] Nonprotein nitrogen (blood)

[2] Uric acid (serum)

[3] Protein (plasma)⁷

[4] Globulin (serum)¹⁸

[5] Albumin globulin ratio

[6] Alkaline phosphatase (serum)

(b) Decrease or no change in⁷

[1] Potassium (plasma)

[2] Phosphorus (serum)

[3] Glutathione⁸

(c) Increase in peptidases (serum)⁵⁷

(d) Increase or no change in
^{47 49 7}

[1] Sugar (blood)^{18 7}

[2] Sodium (plasma)¹⁸

[3] Chloride (plasma)^{18 36 57}

[4] Carbon dioxide (plasma)¹⁸

(e) Decrease in free cholesterol (plasma)⁴⁷

(5) Tolerance tests⁴⁸

(a) Glucose^{8 47 57}

[1] Normal

[2] Diabetic

(b) Insulin — increased resistance⁷

(6) Miscellaneous⁴⁷

(a) Acne

(b) Weight increase

(c) Pitting edema

(d) Blood pressure not affected⁵⁷

(7) Changes observed in patients with various diseases parallel above findings (see 106 III E)

7 Diabetogenic principle

a Introduction

- (1) Diabetogenic effects in the past have been produced largely from crude extracts
- (2) Factors causing diabetes in such extracts have been considered in part due to^{1 5 8 12 16}
 - (a) Growth hormone^{1 16}
 - (b) Thyrotropin
 - (c) Adrenocorticotropin
 - (d) Prolactin

- (3) Purified growth hormone will produce diabetes in
 - (a) Dogs (not puppies)
 - (b) Cats
 - (c) Batrachians

b Carbohydrate metabolism

- (1) Blood sugar increased^{2 3 5 7 9 1 16}
- (2) Liver glycogen maintained⁵
- (3) Carbohydrate utilization inhibited
- (4) Glycosuria produced^{4 5 9 12 15 16}
- (5) Ketonuria (moderate or none)^{4 5 9-1 15 16}

c Fat metabolism

- (1) Production of³
 - (a) Hyperlipemia
 - (b) Hypercholesterolemia
- (2) Oxidation of stored fat increased¹⁶

d Protein metabolism⁵

- (1) Plasma protein level may rise
- (2) Body protein deposition increased
- (3) Nitrogen retention enhanced by the secretory activity of the islets of Langerhans

e Growth accelerated (see above) in puppies causing^{14 16}

- (1) No diabetes with brief trials
- (2) Diabetes in long experiments (and growth cessation eventually)

f Body weight increases^{9-13 16}g Metabolic rate normal¹⁰

h Respiratory quotient lowered (dogs, cats, rats, rabbits)

i Hematinic glutathione increased⁵8 Galactins (animal experiments)^{28 28-30 3 23 25 36}

a Lactogenic hormone (prolactin)

- (1) Mammary glands stimulated
 - (a) Milk secretion (ACTH is probably essential)^{11 4}
 - [1] Initiated
 - [2] Maintained
 - (b) Lobulo alveolar growth may be produced
- (2) Effects on reproductive processes
 - (a) Progesterone formation may (or may not) be dependent on prolactin (questionable in normals)^{1 7 10 13 37}
 - (b) FSH inhibited (birds, rats)
 - (c) Estrus cycle depressed (rats, mice, doves)^{3 6 18 23}
 - (d) Pregnancy³⁴
 - [1] Span may be prolonged (rodents)
 - [2] Prevention by excessive delay in implantation (rodents)
 - (e) Pseudopregnancy can be induced (rats)¹⁸
 - [1] Follicles do not mature
 - [2] Ovulation is inhibited
 - [3] Vagina shows high degree of cornification
 - [4] Endometrium has gestational changes
 - [5] Hypertrophic corpora lutea secrete progesterone
 - [6] Mammary glands show lobulo alveolar development⁶
 - (f) Sexual behavior²⁸
 - [1] Nesting behavior (fish)
 - [2] Parental instincts (rats)
 - [3] Brooding (fowls)

(3) Splanchnomegaly (pigeons) of^{7 8 30}

- (a) Liver
- (b) Pancreas
- (c) Intestine

(4) Growth not affected^{18 3}(5) Nitrogen excretion unaltered (rats)^{18 21}(6) Blood sugar not increased in dogs³⁵

- (7) Basal metabolic rate increased (thyroidectomized pigeons)²¹
- b Mammogen I—stimulates duct growth (animal experiments)^{1 5 11 17}
- c Mammogen II—causes lobulo alveolar growth (may be same as lactogenic hormone) (animal experiments)^{4 11 20 22}
- 9 Adrenomedullotropic principle (?)—"dark cells" of adrenal medulla stimulated without change in chromaffin tissue (hypophysectomized rats)^{1 3}
- 10 Parathyrotropic hormone (?)^{1 4 5}
 - a Parathyroid activity may be increased without change in size as shown by
 - (1) Hyperemia
 - (2) Histologic findings
 - b Hypercalcemia occurs but results are variable^{3 6}
- 11 Splenotropic principle (?)¹
 - a Evidence is not sufficient to distinguish this principle from growth hormone
 - b Splenic size may be increased
- 12 Metabolic factors
 - a Carbohydrate metabolism factors
 - (1) Pancreatropic factor (?)^{2 23 27 28, 33, 36}
 - (a) Probably its effects are produced indirectly through action of glycotropic or diabetogenic factors
 - (b) Stimulation of
 - [1] Islet cells to increase in^{7 21 22}
 - [a] Number
 - [b] Size
 - [c] Insulin production
 - [2] Protein anabolism^{9 25 31 47}
 - [3] Nitrogen retention
 - [4] Body weight gain
 - (c) Blood sugar level decreases usually
 - (2) Contra insular factor (?)
 - (a) Identical with ACTH possibly
 - (b) Blood sugar increases when this factor is injected suboccipitally into cerebrospinal fluid (seems to act through the adrenal cortex)
- (3) Glycotropic (anti insulin) factor (?)
 - (a) Same as ACTH probably²³
 - (b) Anti insulin effect is produced through stimulation of adrenal cortex²³
 - (c) Blood sugar is not converted into muscle or liver glycogen (opposite to insulin effect)^{6 11 17 18 20 22 30 45 46}
 - (d) It may not be identical with^{45 46}
 - [1] Gonadotropin
 - [2] Thyrotropin
 - [3] Prolactin
 - [4] Ketogenic factor
 - [5] Melanophore stimulating factor
- (4) Glycostatic factor (?)^{11 14 16, 29 40}
 - (a) Glycogen storage is increased in
 - [1] Liver
 - [2] Muscles
 - (b) Hyperglycemia in well fed animals
 - (c) Protein catabolism reduced, producing hypoglycemia; amino acids here are only source of carbohydrates in normal fasted rats
- (5) Hyperglycemic factor (?)—liver glycogenolysis occurs with subsequent rise in blood sugar
- (6) Insulotropic principle (?)—insulin producing cells of islets of Langerhans are stimulated directly¹
- b Fat metabolism factors
 - (1) Ketogenic factor (orophysin) (?)^{1 4 8-10 41}
 - (a) May be identical with
 - [1] Growth hormone
 - [2] Diabetogenic factor
 - (b) Is found in preparations of
 - [1] Growth hormone
 - [2] Thyrotropin
 - [3] Prolactin

- (c) Decreases basal metabolic rate
- (d) Increases
 - [1] Output of acetone bodies in blood and urine after diet of butter fat or by fasting, rather than decreased utilization
 - [2] Liver fat deposition
 - [3] Fat catabolism beyond oxidation capacity of body (may be secondary effect) compensating for decreased protein catabolism²⁶
 - [4] Specific dynamic action of protein
- (2) Lipotropic factor (?)³⁴
 - (a) Origin from posterior lobe possibly
 - (b) Blood fat lowered (may be related to TSH)
 - (c) Liver fat is dependent on supply of hormone
 - [1] Decreased by large quantities
 - [2] Increased by moderate amounts
 - (d) Ketogenic factor probably counterbalanced by it
- c Protein metabolism factor (?)¹⁹⁻²⁴
 - (1) Identical with growth factor possibly²⁵
 - (2) Nitrogen excretion decreased
 - (3) Liver protein (alkaline soluble) decreased in 35 to 53 per cent of normal guinea pigs
 - (4) Regulation of blood amino acids
- d Water metabolism factor (?) has a diuretic action^{12 15 33 37 38 42}
 - (1) Thyroid gland is necessary for this function⁴³
 - (2) Antidiuretic factor of posterior lobe neutralizes it
- Calcium factor (?) regulates the calcium level, but the parathyroids must be present (see 2 VI B 10)
- 13 Renotropic factor (?)
 - a Kidney tissue atrophy may be prevented (following unilateral ligation of ureter in female rats)^{1 2}
- b Renal tubular cells show
 - (1) Hyperplasia
 - (2) Hypertrophy
- c Glomerular size increased
- d Note that
 - (1) Thyroxin acts as a synergist⁴
 - (2) Thyroidectomy is antagonistic to these effects⁵
- 14 Hepatic and cardiac factors (?)¹
 - a These are considered independent of growth hormone
 - b Liver and heart have disproportional hypertrophy in comparison with bodily enlargement (bones, muscles)
- 15 Hematopoietic factor (?)^{1 2}
 - a Same as ACTH possibly
 - b Action may be
 - (1) Directly on bone marrow
 - (2) Indirectly on
 - (a) Thyroid
 - (b) Adrenals
 - (c) Testes
 - c Hemoglobin is decreased
 - d Red blood cells and reticulocytes are increased
- 16 Specific metabolic factor (?)^{1 7 9 16}
 - a Comment
 - (1) Its presence has been demonstrated in most species (although doubtful in humans) by simple extracts of
 - (a) Pituitary tissue
 - (b) Dissected anterior or posterior lobes
 - (2) Concentration is greatest in
 - (a) Pituitary colloid
 - (b) Intermediate lobe
 - (3) Separation from the melanophore stimulating (expanding) hormone has not yet been successful
 - (4) Ketogenic and adrenalin inhibition factors are not identical with it
 - (5) All animals do not react to this principle and others show no resistance to repeated injections
 - (6) Specific actions although not clearly defined, have been demonstrated in animals that are
 - (a) Normal
 - (b) Hypophysectomized

- (c) Thyroidectomized
- (d) Adrenalectomized

(7) Exophthalmos is not produced⁴

b Decreases

- (1) Carbohydrate oxidation
- (2) Insulin sensitivity
- (3) Hyperglycemia of adrenalin
- (4) Respiratory quotient
- (5) Nitrogen retention

c Increases

- (1) Basal metabolic rate independent of the thyroid gland (humans rabbits rats guinea pigs)
- (2) Oxygen consumption (humans animals—fasted or fed)
- (3) Carbon dioxide production especially in fasted animals
- (4) Body temperature
- (5) Gluconeogenesis (possibly)
- (6) Glycosuria and ketonuria (Housay dogs)
- (7) Glycolytic action (rats guinea pigs, rabbits)
- (8) Fat metabolism
- (9) Ketonemia (fasted rats)

17 Chromatophore stimulating or expanding factor (?) (melanophore erythrophore)^{1 2 17 20-22}

a Comment

- (1) Although the presence of this factor in humans has not been demonstrated it probably exists in all other vertebrates either singly or as a part of another hormone
- (2) Each name above refers to the specific type of pigment cell that responds to stimulation by the factor

b Pigmentation is controlled by

- (1) Melanophore stimulating factor which produces darkening of the animal by dispersion of melanin granules (melanosomes) in pigment cells (melanophores) of lower vertebrates as^{1 2 5 8 1 13 15 17 20 22}
 - (a) Fish (specific types)
 - (b) Amphibia
 - (c) Reptiles

(2) Erythrophore stimulating factor expands the red granules (erythrosomes) of pigment cells (erythrophores) in certain fish

- c Formation of new melanin (questionable)^{3 11}
- d Adaptation to darkness by retinal pigment cells is accelerated⁴
- e Body temperature may be increased (rabbits)¹⁰
- f Adrenal cortical hypertrophy (rabbits, rats guinea pigs)^{9 11}
- g Hyperglycemia may occur (rabbits)¹⁰
- h No effect on¹⁰
 - (1) Blood pressure
 - (2) Basal metabolic rate
 - (3) Liver glycogen
- i Water excretion—variable results^{12,19}

18 Vasopressin

a Comment

- (1) The postulated principles of the posterior lobe have not been purified sufficiently to permit accurate analysis of their specific actions
- (2) Many factors are involved in the results obtained as
 - (a) Species of animal
 - (b) Concentration of material
 - (c) Duration of experiment
- (3) A single protein hormone may contain all three factors

b Smooth muscle^{14 21 27 37 41 45 2, 46}

- (1) Small and large bowel activity is increased, but inhibition of movements in some portions may occur (variable reports)
- (2) Defecation is aided
- (3) Gastric motility is decreased
- (4) Gallbladder is contracted (depends on its physiologic state)
- (5) Bronchi are stimulated (not a specific action probably due to contamination)
- (6) Uterus is stimulated^{43 47}
 - (a) Response according to physiologic state
 - (b) Most effective in nonpregnant uterus or early pregnancy
- (7) Blood vessels are constricted

- c Cardiovascular
- (1) Muscle fibers of blood vessels contracted directly¹⁶ ^a
 - (2) Blood pressure
 - (a) Rise, if any, is insignificant (no effect in normal humans)⁴⁷ ^b
 - (b) Momentary drop is produced by a decreased coronary blood flow
 - (3) The following are increased, after a temporary fall ⁴ ⁴⁶
 - (a) Pulse rate
 - (b) Cardiac output
 - (c) Oxygen consumption
- d Respiration¹ ¹⁹ ²⁵ ⁹
- (1) Acceleration usually
 - (2) Periods of apnea may be due to secondary circulatory effects on the respiratory center
- e Kidneys (see 2 VI B 20)
- (1) Urinary volume markedly reduced in normal individuals with high water intake by absorption at⁴ ⁸ ⁷⁰ ²¹ ⁷⁹ ⁴⁰ ⁴² ⁴⁰ ⁵⁰ ⁵⁸ ⁶⁰ ⁵⁸
 - (a) Proximal convoluted tubule
 - (b) Thin portion of Henle's loop (see 8 VI)
 - (2) Tubular chloride reabsorption remains the same¹⁰ ¹⁵ ⁴⁰
 - (3) Glomerular filtration rate increased¹⁰
 - (4) Plasma flow maintained effectively
 - (5) Water center (questionable) in hypothalamus inhibited (see 88 VI C 6)⁴⁸
 - (6) Glycosuria may occur in certain species³ ¹⁷ ²⁸ ³⁴ ⁶³ ⁶
- f Gastro intestinal secretions inhibited ⁶ ³⁰ ⁵ ⁵⁷ ⁵⁸
- g Central nervous system³⁸
- (1) Autonomic centers adjacent to ventricles stimulated
 - (2) Marked vasodilation may be produced at blush area with an injection into cerebral ventricles (man monkey)
- h Blood
- (1) Leukocytes increased¹¹
 - (2) Coagulation prolonged (questionable)⁹
- (3) Dilution causes a decrease in ² ¹¹
 - (a) Hematocrit
 - (b) Specific gravity
 - (4) Hyperglycemia produced in certain species (an unidentified principle may cause this action)¹⁷ ¹⁸ ³ ³⁵ ⁴¹ ⁶⁴
 - (a) Antagonistic to insulin and epinephrine⁵ ⁷ ¹ ⁷³ ⁸¹ ⁶
 - (b) Glycotropic effect by formation of glycogen from carbohydrate sources (fasted rats, guinea pigs rabbits very little action in mice)¹
 - (5) Protein (serum) decreased⁶⁸
 - (6) Phosphate (inorganic, serum) elevated¹⁷
 - (7) Lipid substances show no significant changes³⁰ ⁵⁴
- 19 Oxytocin
- a Smooth muscle (variable results, dosage and method of administration important)
- (1) Intestine (large) shows inhibition of¹³ ¹⁴
 - (a) Tone
 - (b) Peristalsis
 - (2) Uterus¹ ⁷ ¹¹ ¹⁵ ¹⁶ ¹⁹
 - (a) Stimulation by direct action on myometrium
 - [1] Maximal effect (variable results) at parturition
 - [2] Slight change during first half of menstrual cycle
 - [3] All portions are not affected simultaneously
 - (b) Small amounts of principle
 - [1] Muscular tone augmented
 - [2] Amplitude of contractions increased
 - (c) Large amounts of principle may produce tetany (not in rabbits dogs)
- b Kidneys ³ ⁶ ^{1*}
- (1) Excretion
 - (a) Creatine decreased
 - (b) Phosphate (inorganic) decreased
 - (c) Chloride increased

- (c) Thyroidectomized
- (d) Adrenalectomized
- (7) Exophthalmos is not produced^a
- b Decreases
 - (1) Carbohydrate oxidation
 - (2) Insulin sensitivity
 - (3) Hyperglycemia of adrenalin
 - (4) Respiratory quotient
 - (5) Nitrogen retention
- c Increases
 - (1) Basal metabolic rate independent of the thyroid gland (humans rabbits, rats guinea pigs)
 - (2) Oxygen consumption (humans, animals—fasted or fed)
 - (3) Carbon dioxide production, especially in fasted animals
 - (4) Body temperature
 - (5) Gluconeogenesis (possibly)
 - (6) Glycosuria and ketonuria (Houssay dogs)
 - (7) Glycostatic action (rats guinea pigs rabbits)
 - (8) Fat metabolism
 - (9) Ketonemia (fasted rats)
- 17 Chromatophore stimulating or expanding factor (?) (melanophore erythrophore)^{1 2 17 20 22}
 - a Comment
 - (1) Although the presence of this factor in humans has not been demonstrated, it probably exists in all other vertebrates either singly or as a part of another hormone
 - (2) Each name above refers to the specific type of pigment cell that responds to stimulation by the factor
 - b Pigmentation is controlled by
 - (1) Melanophore stimulating factor which produces darkening of the animal by dispersion of melanin granules (melanosomes) in pigment cells (melanophores) of lower vertebrates as^{1 2 8-8 1 11 1 17 20 22}
 - (a) Fish (specific types)
 - (b) Amphibia
 - (c) Reptiles
 - (2) Erythrophore stimulating factor expands the red granules (erythrosomes) of pigment cells (erythrophores) in certain fish
- c Formation of new melanin (questionable)^{3 14}
- d Adaptation to darkness by retinal pigment cells is accelerated¹
- e Body temperature may be increased (rabbits)¹⁰
- f Adrenal cortical hypertrophy (rabbits rats, guinea pigs)^{9 11}
- g Hyperglycemia may occur (rabbits)¹⁰
- h No effect on¹⁰
 - (1) Blood pressure
 - (2) Basal metabolic rate
 - (3) Liver glycogen
- i Water excretion—variable results^{13 19}
- 18 Vasopressin
 - a Comment
 - (1) The postulated principles of the posterior lobe have not been purified sufficiently to permit accurate analysis of their specific actions
 - (2) Many factors are involved in the results obtained as
 - (a) Species of animal
 - (b) Concentration of material
 - (c) Duration of experiment
 - (3) A single protein hormone may contain all three factors
 - b Smooth muscle^{14 1 7 36 37 41 42 44}
 - (1) Small and large bowel activity is increased, but inhibition of movements in some portions may occur (variable reports)
 - (2) Defecation is aided
 - (3) Gastric motility is decreased
 - (4) Gallbladder is contracted (depends on its physiologic state)
 - (5) Bronchi are stimulated (not a specific action probably due to contamination)
 - (6) Uterus is stimulated^{43 47}
 - (a) Response according to physiologic state
 - (b) Most effective in nonpregnant uterus or early pregnancy
 - (7) Blood vessels are constricted

- White blood cells^{21 89}
 - (1) No change
 - (2) Leukopenia slight, with eosinophilia
- d Color index increased (questionable if a, b, c and d are due to hypophysectomy alone)
- Reticulocytes decreased usually^{85 88 97 177}
- f Response to bleeding similar to normal rats with an increase in³⁰
 - (1) Red blood cells
 - (2) Hemoglobin
 - (3) Reticulocytes
- 5 Urinary excretion
 - Decreased
 - (1) Nitrogen, results variable (dogs rats, toads)^{71 74}
 - (2) Uric acid (dogs, rats on ordinary or nitrogen free diet)
 - (3) Creatinine (dogs rats)¹
 - (4) Purine bases (dogs rats on ordinary or nitrogen free diet)
 - (5) Ketones (dogs)⁸⁶
 - (6) Chlorides (rats)
 - b Increased (rats)
 - (1) Sodium
 - (2) Potassium
 - (3) Calcium
 - c Urobilin normal (dogs)
 - d Polyuria produced (dogs, rats, toads)
 - e Diuretic response to water is delayed (rats)⁶⁰
 - f Clearance tests (inulin diodrast) (dogs)^{130 131}
 - (1) Fifty per cent or more reduction
 - (2) Results indicate a decrease in
 - (a) Tubular activity
 - (b) Renal blood flow
- 6 Blood chemical analyses
 - a Potassium (plasma) (dogs)^{38 76 77}
 - (1) Normal
 - (2) Decreased (amphibia)
 - b Calcium
 - (1) Variable reports (toads dogs rats)^{1 37 43 69 69 77 96 116}
 - (2) No change probably in humans
 - Phosphorus, inorganic (dogs)^{38 66 76 77}
 - (1) Normal
 - (2) Decreased
 - d Iodine (protein bound) decreased^{9 14}
 - (1) Fifty per cent decrease in rats by the third day
 - (2) Initial rise and then a fall in dogs due to change from hyperthyroid to ■ hypofunctional state
 - Phosphatase (serum) (dogs)^{37 53 66 67}
 - (1) Normal
 - (2) Decreased
 - f Magnesium (dogs)^{38 76 77}
 - (1) Normal
 - (2) Decreased
 - g Fatty acids total fats and cholesterol (dogs)^{34 110}
 - (1) Decreased
 - (2) Increased (rats)
 - h Amylase activity increased (dogs)²¹
 - i No change in the following (dogs)^{38 76 77}
 - (1) Nonprotein nitrogen
 - (2) Sodium
 - (3) Chlorides
 - (4) Carbon dioxide
 - 7 Fecal excretion
 - a Decreased chlorides (rats)
 - b Increased
 - (1) Calcium
 - (2) Phosphorus
 - 8 Carbohydrate metabolism
 - a Carbohydrate absorption from intestine may be altered due to secondary hypothyroidism⁹⁴
 - (1) Normal (toads)^{5 7}
 - (2) Decreased (rats)^{83 108}
 - b Pancreas
 - (1) Normal amounts of insulin produced—variable reports^{10 41 51 58 133}
 - (2) If rat ■ well fed, insulin content of pancreas is normal⁴
 - c Diabetes (experimental) may be lessened by removal of pancreas
 - d Insulin sensitivity becomes extreme^{23 36 59 133}
 - Muscle glycogen^{23 106}
 - (1) Normal
 - (2) Decreased
 - f Liver glycogen ■^{73 105}
 - (1) Content
 - (a) Normal
 - (b) Decreased²⁵

- (2) Glomerular filtration rate increased
- (3) Plasma flow increased
- Hyperglycemia ■ produced in certain species which may or may not be antagonistic to insulin action⁶ ⁸⁻¹⁰ ■ ⁷⁰
- d Secretion of milk is increased in lactating animals (humans, too but of no clinical value)¹⁷
- Oxygen consumption slightly decreased
- 20 Antidiuretic principle (?) (may be a part of pitressin⁴)
 - a Water metabolism regulated¹ ² ⁶ ¹¹
 - (1) Action directly on descending loop of Henle
 - (2) Control of reabsorption of chlorides
 - Salt and water balance controlled (not definitely established a relationship exists between posterior lobe and adrenals)² ⁷⁻¹³
- 21 Other posterior lobe principles (questionable)
 - a Lipotrin (?)—origin not confirmed (see 2 VI B 2 and 12)
 - b Adrenalin inhibition factor (?)¹⁻³
 - (1) Separate factor
 - (2) Epinephrine action may be inhibited
 - c Hyperglycemic factor (?) (certain species only)
 - (1) Insulin antagonism
 - (2) Glycotropic effect
- C HYPOPHYSECTOMY (see 2 VI)⁴⁴⁻⁴⁹ ¹ ⁶
 - 1 Introduction
 - a Literature on the removal of the pituitary gland is contradictory and confusing
 - b The results are often due to brain injury rather than the hypophysectomy
 - c Other factors regarding the animal must be considered in each experiment as
 - (1) Species
 - (2) Age
 - (3) Care
 - (4) Diet
 - d Many survive for several months and demonstrate that the pars glandularis is the most essential portion of the mammalian pituitary
 - 2 All body and skeletal development particularly ceases in young animals¹ ²⁴ ⁸¹ ■ ¹¹⁸
 - 3 Atrophy of most glands and organs¹ ²¹ ²⁹ ■ ¹¹ ¹¹³ ¹¹⁹⁻¹²¹
 - a Thyroid⁹ ⁹ ³²
 - (1) Greater iodine and thyroxine iodine content than in normal or partially hypophysectomized (dogs)
 - (2) Basal metabolic rate decreased (dogs rats and toads)
 - b Parathyroids (variable reports)⁵ ¹¹⁸ ¹⁹ ⁶² ⁶⁷ ¹¹⁹⁻¹²¹
 - c Adrenals⁴ ¹⁸ ⁸⁹⁻⁹² ⁹⁴ ¹¹⁷
 - (1) Cortical
 - (a) Atrophy
 - (b) Will not hypertrophy even under stress⁶⁴ ¹¹ ¹¹³
 - (2) Medulla unaffected
 - d Gonads and accessory reproductive organs are affected¹⁵ ⁶³ but ripening and segmentation of ovum may take place (rats)⁷⁰ ¹³⁴
 - e Pancreas
 - (1) Islets of Langerhans hypertrophy¹ ⁵
 - (2) Beta cells are
 - (a) Normal
 - (b) Hyperactive
 - (3) Weight is
 - (a) Normal
 - (b) Decreased³¹ ⁸⁸
 - f Pineal unchanged
 - g Liver
 - h Spleen ⁸ ⁹⁰ ⁹⁹ ¹²⁵
 - i Viscera (small), except kidneys³¹
 - j Lymphoid tissue
 - (1) Thymus—variable data, atrophy may be an indirect effect from surgical shock⁵ ⁶⁸ ⁹⁹ ¹⁰⁰ ¹²²
 - (2) No involution in rats¹¹² ¹²⁴
 - k Bone marrow
 - (1) Hypoplastic usually
 - (2) White blood cell formation ■ not greatly impaired
 - 4 Hematologic findings
 - a Red blood cells decreased ⁴ ⁶¹ ⁷⁹ ¹²⁷
 - b Anemia absent (rats)

- 13 Vitamin C content (male and female rats) is decreased in¹²⁵
 - a Adrenals
 - b Testes
 - c Liver
 - d Kidneys
 - Serum
- 14 Pregnancy
 - Early
 - (1) Abortion
 - (2) Fetal resorption
 - b Late
 - (1) Period of gestation unchanged
 - (2) Stillbirth usually
 - c Parturition
 - (1) Normal
 - (2) Milk secretion slight after delivery
 - d Postpartum lactation stops
- 15 Hypophysectomy plus pancreatectomy (Houssay animal)^{46 50 53 55 60 133}
 - a Excretion effects
 - (1) Polyuria
 - (a) Decreased
 - (b) Absent
 - (2) Glycosuria
 - (a) Decreased
 - (b) Absent
 - (3) Nitrogen does not show usual increase
 - b Blood chemical analyses
 - (1) Amylase activity normal (dogs)²
 - (2) Decreased
 - (a) Sugar (animals may die of hypoglycemia shock)
 - (b) Cholesterol
 - (c) Sodium
 - (d) Potassium
 - (e) Calcium
 - (f) Chlorides
 - (g) Total lipids
 - (3) Alkaline reserve
 - (a) Normal
 - (b) Decreased
 - (4) Ketone bodies
 - (a) Small quantities
 - (b) Absent
 - c Carbohydrate metabolism
 - (1) Glucose tolerance curve usually quite low
 - (2) Carbohydrate produced by glycogenesis is utilized
 - (3) Respiratory quotient may increase after ingestion of glucose
 - (4) Glycogen ■ normal in
 - (a) Liver
 - (b) Muscles
 - (5) Insulin causes
 - (a) Extreme hypoglycemia
 - (b) Decreased life expectancy
- d Protein catabolism is slightly increased
- e Basal metabolic rate is not raised
- f Parathyroids degenerate
- g Susceptibility to infection decreases
- h Wounds heal more rapidly
- i Comparison with ■ hypophysectomized animal shows that
 - (1) Survival period is increased
 - (2) Weight loss occurs more slowly
- 16 Hypophysectomy plus thyroidectomy
 - a Liver demonstrates all degrees of cirrhosis even on adequate diets (dogs) (see 2 VI C 11, VIII ■ 1c)¹⁷
 - b Lipid concentration (dogs) of the following (thyroid deficiency alone will do the same) is increased^{17 26 7}
 - (1) Total fatty acids
 - (2) Phospholipids
 - (3) Cholesterol (free and esterified)
 - c Vitamin C of adrenals is decreased as with hypophysectomy alone¹⁻³
- 17 Hypophysectomy plus splenectomy
 - a Red blood cells increase⁸
 - b Hemoglobin increases
 - c Leukocyte count is unchanged⁸⁹
 - d Reticulocytes decrease⁷⁹
- D HYPERHORMONAL EFFECTS (see 2 VI)
- 1 On various organs and functions are summarized under
 - a Individual hormones
 - b Gigantism
 - c Acromegaly
 - d Cushing's syndrome
 - e Pituitary and chorionic hormones
 - f Diabetes mellitus
- 2 On other endocrine glands
 - a Growth hormone¹
 - (1) Thyroid
 - (a) Size—increased
 - (b) Hyperplasia—absent
 - (2) Parathyroids—possible increase in size

- (2) No liberation as glucose into blood stream
- (3) Mobilization impaired by secreted adrenalin^{10 11}
- g Peripheral oxidation of carbohydrates is accelerated but is not due to^{103 104}
 - (1) Increased deposition of muscle glycogen
 - (2) Lactic acid production
- h Blood sugar is normal on an adequate diet, otherwise subnormal^{105 113}
- i Glucose tolerance tests¹⁰⁷
 - (1) Oral—generally increased
 - (2) Intravenous⁷
 - (a) Normal
 - (b) Decreased (rats)
- j Epinephrine effects less pronounced variable results
- k Gluconeogenesis from proteins is decreased⁶
- 9 Fat metabolism
 - a Cachexia may be
 - (1) Produced partly from fat loss in majority of animals
 - (2) Variable depending on experimental animal and diet
 - b Slight change in dogs
 - (1) Total fats
 - (2) Fatty acids
 - (3) Cholesterol
 - c Ketonuria decreased (dogs)
- 10 Protein metabolism
 - a Endogenous source^{13 15}
 - (1) Catabolism decreased
 - (2) Storage decreased in
 - (a) Liver
 - (b) Muscles
 - b Exogenous supply^{71 92, 100 111}
 - (1) Metabolism increased
 - (2) Storage decreased
 - c Specific dynamic action
 - (1) Increased relatively because of lowered basal metabolic rate (dogs)^{1 3 33 9}
 - (2) Decreased (rats)³²
 - d Globulins (plasma) increased (dogs)^{7 83}
 - e Albumin (plasma) increased (dogs rats)⁸³
 - f Viscosity (plasma) increased (dogs)
 - g Liver arginase activity decreased³³
- 11 General effects
 - a Glutathione decreased in
 - (1) Red blood cells
 - (2) Liver⁷³
 - (3) Muscles
 - b Muscular
 - (1) Activity subnormal
 - (2) Phosphocreatin decreased (toads 33%)
 - c Sensitivity increased to^{90 91}
 - (1) Infection
 - (2) Trauma
 - d Blood pressure^{93 15}
 - (1) Markedly lowered
 - (2) More sensitive (rats) to renin than normal or adrenalectomized animals
 - e Lactation inhibited^{34 83}
 - f Cutaneous pallor (animals) due to^{2 118}
 - (1) Contraction of melanophores
 - (2) Expansion of xanthophores
- 12 Observations with fasting and various diets
 - a Fasting
 - (1) Blood sugar^{39 7 83}
 - (a) Very low
 - (b) Hypoglycemia reactions of ten, may be fatal
 - (2) Glycogen decreased in^{74 101 107}
 - (a) Liver
 - (b) Muscles
 - (3) Gluconeogenesis from protein decreased
 - (4) Decreased excretion of
 - (a) Nitrogen (dogs^{13 14} toads⁵ rats¹)
 - (b) Creatinine (marked)
 - (c) Phosphate
 - b Protein free diet
 - (1) Decreased excretion of
 - (a) Uric acid
 - (b) Creatinine (marked)
 - (c) Purine bases
 - (d) Phosphate
 - (2) Protein catabolism decreased (dogs)
 - c Meat diet
 - (1) Nitrogen elimination normal/kg/day (dogs rats)
 - (2) Phosphate excretion normal
 - (3) Creatinine output slightly increased (dogs, rats)^{13 14}

- Intermediate lobe
 - (1) Secretions probably occur from its cellular remnants
 - (2) Animals without this lobe may be dependent on other portions of pituitary gland
- d Posterior lobe
 - (1) Most likely forms its own principles but problem is unsettled
 - (2) Anterior or intermediate lobes may be original source of secretions
- 2 Pathway of secretions²⁰
 - a Anterior lobe—hormones pass directly into the blood stream
 - b Intermediate lobe—hormones may leave by the infundibular stalk (varies with species)
 - c Posterior lobe principles
 - (1) Enter cerebrospinal fluid of ventricle
 - (2) Diffuse through nervous tissue
 - (3) Act on parasympathetic center (tuber cinereum) in hypothalamus
- 3 Pituitary content of the different hormones (human)
 - a Gonadotropic hormones^{16, 23, 27}
 - (1) Fetus
 - (a) FSH—small amount
 - (b) LH—absent
 - (2) Children have small quantities
 - (3) Reproductive age—males have hypophyses with a potency 4 times that of females
 - (4) Old age
 - (a) Males—variable may have same values as castrates
 - (b) Females—high concentrations
 - (5) Castrates—large amounts
 - b Thyrotropic hormone (TSH)^{3, 27, 31}
 - (1) No alteration in concentration with
 - (a) Age
 - (b) Other factors i.e. pregnancy
 - (2) Average range of concentration within pituitary is 5 to 30 guinea pig units (see 2 VIII D 2)
 - c Lactogenic hormone—shows no change with⁷
 - (1) Age
 - (2) Sex
 - d Chromatophore (melanophore) stimulating hormone (?) content is unaltered by^{1, 46}
 - (1) Age
 - (2) Sex
- F ACTIVITY AT DIFFERENT PERIODS IN LIFE
 - 1 Intrauterine
 - a Little is known concerning the role of fetal hormones in the presence of placental hormones
 - b It is possible that certain pituitary hormones may go through the placenta
 - 2 Infancy and childhood—all known hormones are active, except
 - a Gonadotropic
 - b Adrenocorticotrophic
 - (1) If it controls all factors of adrenal cortex, an uneven response occurs for
 - (a) Hair growth is limited
 - (b) Relative lymphocytosis ■ present
 - (c) Salt hormone effects may be normal
 - (d) 17 ketosteroids are low
 - (e) Urinary 11 oxysteroids are same as adult
 - (2) Variation in above may be due to independent (or pituitary ACTH) level of adrenocortical activity
 - c Lactogenic
 - 3 Puberty
 - a Growth rate increases, probably due to a combined action of following hormones
 - (1) Growth
 - (2) Thyroid
 - (3) Adrenocortical
 - (4) Testosterone
 - (5) Female hormones indirectly
 - b Gonadotropic (FSH and LH) production increases with activation of basophilic cells
 - c ACTH may stimulate adrenal cortices to initiate sexual hair growth
 - 4 Menstruation
 - Germ cell development is due to FSH causing
 - (1) Follicle formation
 - (2) Estrogen production
 - b At ovulation FSH increases

- (3) Adrenals (entire)—no change (rats)
- (4) Pancreatic islets
 - (a) No change (puppies)
 - (b) Diabetes (adult dogs)
- (5) Testes—no change (rats)
- (6) Ovaries—no change (rats)
- b Follicle stimulating hormone
 - (1) Increase in weight of
 - (a) Testes
 - (b) Ovaries
 - (2) Other glands—no data
- c Luteinizing hormone
 - (1) Testes—Leydig cell hyperplasia (see 2 V I B 4)
 - (2) Ovaries—luteinization (see 2 V I B 4)
 - (3) Other glands—no data
- d Thyrotropin
 - (1) Thyroid—hyperplasia
 - (2) Other glands—no data
- e Adrenocorticotropin
 - (1) Adrenal cortices—hyperplasia
 - (2) Other glands—see 2 V I B 6 b (9)
- 3 Posterior lobe extracts
 - a Variable results depending on many factors especially the composition of the preparation²³
 - b Mucous membranes of stomach and lungs show areas of^{1 2 6-9 11 18 22}
 - (1) Hemorrhage
 - (2) Necrosis
 - (3) Ulceration
 - c Secretions of the following are decreased⁴
 - (1) Pancreas
 - (2) Stomach
 - (3) Saliva
 - d Galactagogue in certain species
 - e There is a decrease in
 - (1) Lymph flow
 - (2) Cerebrospinal fluid
 - f Cardiac hypertrophy (guinea pigs)²⁷
 - g Blood pressure—angiospasm of renal arteries and arterioles may produce pathologic lesions^{4 20}
 - h Intraocular pressure may fall¹³
 - i Renal influence on excretion of minerals is variable except for an increase in^{10 17}
 - (1) Sodium
 - (2) Chloride

- j Role in hypertension and toxemia of pregnancy is not known
- k Testicular growth may be depressed with injury to the tubular epithelium²³
- l Liver
 - (1) Fat may increase⁵
 - (2) Glycogen mobilization^{14 26}
- m Weight loss
- n Blood
 - (1) Red cells may increase in circulation^{6 7}
 - (2) Anemia may be severe^{6 7 11 16}
 - (3) Hematocrit may fall^{6 7}
 - (4) Volume may decrease
 - (5) Chemical analyses
 - (a) Decrease in
 - [1] Protein (total)
 - [2] Cholesterol (doubtful significance)^{10 21}
 - [3] Calcium (by intravenous administration)
 - [4] Fat (questionable)^{10 21}
 - (b) Increase in
 - [1] Potassium¹⁰
 - [2] Lactic acid but does not parallel blood sugar^{3 12}

E HISTOPHYSIOLOGY

- 1 The cellular origin of secretions (a summary of opinions)
 - a Introduction
 - (1) The following data are based on clinical and experimental evidence^{1 24 36 4 44}
 - (2) Pituitary hormones may be secreted in groups rather than singly¹³
 - b Anterior lobe
 - (1) Acidophilic cells may secrete the following hormones
 - (a) Growth (somatotropic)^{28 30 49 4}
 - (b) Luteinizing (LH or prol. B)^{9-11 31 38 41}
 - (c) Luteotropic^{2 41}
 - (d) Lactogenic^{1 4 70 73 35}
 - (2) Basophilic cells may secrete the following hormones
 - (a) FSH (possibly from acidophils)^{1 4 6 11 70 73 31-38 45}
 - (b) TSH^{10 11 6 33}
 - (c) ACTH^{3 16 17 19 37 43}

b Follicle stimulating hormone (sheep and hog pituitary glands)^{5 6 14}

(1) Molecular weight 70,000

(2) Isoelectric point (swine) 4.8

(3) Contents (a glycoprotein)

(a) Hog

PER CENT

[1] Mannose 4.5

[2] Hexosamine 4.4

(b) Sheep

PER CENT

[1] Carbohydrate 10.13

[2] Hexosamine 8.0

(4) Properties

(a) Destroyed by

[1] Ptyalin

[2] Takadiastase

[3] Amylase

(b) Soluble in water

(c) Relatively stable toward trypsin

(d) Relatively heat stable

c Luteinizing hormone (metaletrin, LH, ICSH)^{7 8 17 18 20 27}

(1) Sheep pituitary glands

(a) Molecular weight 40,000

(b) Isoelectric point 4.6

(c) Contents which have been determined

PER CENT

[1] Nitrogen 14.2

[2] Hexosamine 5.8

[3] Carbohydrate 4.5

[4] Mannose 4.5

[5] Tyrosine 4.5

[6] Tryptophane 1.0

(2) Swine pituitary glands

(a) Molecular weight 100,000

(b) Isoelectric point 7.45

(c) Contents which have been determined

PER CENT

[1] Carbon 49.37

[2] Nitrogen 14.93

[3] Hydrogen 6.83

[4] Tryptophane 3.8

[5] Mannose 2.8

[6] Hexosamine 2.2

[7] Carbohydrate 2.0

(3) Properties common to both

(a) Destroyed by proteolytic enzymes

(b) Not destroyed by

[1] Amylolytic enzymes

[2] Ptyalin

[3] Takadiastase

(c) Inactivated by

[1] Ketene

[2] Cysteine

d Thyrotropic hormone (sheep and beef pituitary glands) ≈ 35

(1) Molecular weight 10,000

(2) Contents which have been determined

PER CENT

(a) Carbon 45.6

(b) Nitrogen 12.6 or 13

(c) Hydrogen 6.09

(d) Hexose 3.5

(e) Glucosamine 2.5

(f) Sulfur 1.0

(g) Phosphorus 0

(h) Carbohydrate grouping

(3) Properties

(a) Soluble in water and aqueous solutions of

[1] Alcohol

[2] Acetone

[3] Pyridine

(b) Insoluble in

[1] Alcohol

[2] Chloroform

[3] Methanol

[4] Hexachloroethane

[5] Acetone

[6] Ether

[7] Pyridine

(c) Precipitated from aqueous solution by the following acids

[1] Phosphotungstic

[2] Flavanic

[3] Picric

[4] Mercuric chloride

(d) Not precipitated by dilute solutions of

[1] Lead acetate

[2] Sulfosalicylic acid (?)

[3] Trichloroacetic acid (?)

(e) Absorbed by

[1] Protein precipitants

[2] Colloidal ferric hydroxide

[3] Benzoic acid

[4] Animal charcoal

[5] Permutit

- c LH (see 57 VI B 1, 2 58 III A Chart 108 p 947)
- (1) Secretion rises slowly, following menstruation until ovulation
 - (2) Corpus luteum stimulated for progesterone formation
- d Luteotropic hormone maintains progesterone secretion
- Vasopressin activity on uterine muscle at
- (1) Ovulation (possibly)
 - (2) Menstruation
- 5 Maturity
- a All pituitary hormones except growth are at their maximum integration
 - b Gonadotropins vary with
 - (1) Menstrual cycles
 - (2) Pregnancy
 - c Gonadal hormones exert their pituitary control by
 - (1) Inhibition
 - (2) Stimulation
- 6 Pregnancy
- a FSH activity inhibited
 - b Cellular changes in pituitary (see 2 V D 2)
 - c Lactogenic hormone stimulated by withdrawal of placental hormones
 - d Oxytocic principle increases (rabbits)
- 7 Climacteric
- a Gonadotropic hypersecretion
 - (1) Males—rarely
 - (2) Females—fairly common
 - b Other hormones are still active, including perhaps small amounts of growth hormone
- 8 Old age
- a Gonadotropins
 - (1) Males—show a decline
 - (2) Females—persist or increase
 - b All remaining hormones probably decrease
- 2 Preparation (commercial)
- a Variable methods exist for hormonal
 - (1) Extraction
 - (2) Purification
 - b Separation of pituitary hormones is accomplished by analysis of their chemical properties
- 3 Hormones which are now considered possible to isolate in chemically pure form or nearly so
- a Growth^{1 23}
 - b Follicle-stimulating (thylakentrin)^{6 14}
 - c. Luteinizing (metakentrin)^{7 8 17 18 20}
 - d Thyrotropic^{1 2 10 21}
 - e Adrenocorticotrophic^{1 12 21 23 25}
 - f Lactogenic²¹
- 4 Chemical analysis
- a Growth hormone (or pituitary glands)^{5 13 16}
 - (1) Molecular weight 47,300 \pm 600
 - (2) Isoelectric point 6.85
 - (3) Contents which have been determined

	PER CENT
(a) Carbon	46.35
(b) Nitrogen	15.65
(c) Glutamic acid	13.40
(d) Hydrogen	7.07
(e) Tyrosine	4.3
(f) Methionine	3.06
(g) Cystine	2.25
(h) Sulfur	1.3
(i) Tryptophane	0.92
(j) Carbohydrate	11
 - (4) Properties
 - (a) Destroyed by
 - [1] Pepsin
 - [2] Trypsin
 - (b) More stable in alkali than acid medium
 - (c) Unstable at boiling water temperature
 - (d) Retained biologic activity in urea solutions
 - (e) In buffer of pH7
 - [1] Protein is coagulated at from 70° to 80°
 - [2] Growth potency is destroyed

VII CHEMISTRY

A ANTERIOR LOBE

1 Structure of hormones

- a Exact chemical formulas are unknown
- b Protein molecules are the basic units of structure

- (2) Amino acids which are present
 (a) Cystine
 (b) Tyrosine
 (c) Arginine

	PER CENT
(3) Carbon	48.64
(4) Nitrogen	15.00
(5) Oxygen	22.89
(6) Hydrogen	6.63
(7) Sulfur	3.00
■ Properties—activity destroyed by	
(1) Dilute acids	
(2) Alkalis	
(3) Enzymes of gastro intestinal tract	

VIII BIO ASSAY

A INTRODUCTION

- 1 Unknown preparation of the hormone is injected into different types of animals under special conditions
- 2 Many of the tests are difficult to perform
- 3 Results are variable

B GROWTH HORMONE

- 1 Methods (rats usually employed)
 - a Hypophysectomized (male or female) animals are used to determine
 - (1) Resumption of body growth^{1 13}
 - (2) Weight gain^{1 13}
 - (3) Increase in tail length^{8 11}
 - (4) Change in width of uncalcified cartilage at proximal epiphysis of tibia^{4 9 14}
 - b Resumption of body growth in normal plateaued females³
 - Other less frequent experiments by finding
 - (1) Decrease in the following¹¹
 - (a) Glutathione content of liver¹⁰
 - (b) Nitrogen excretion
 - (c) Urea (blood and tissues)
 - (d) Amino acids of
 - [1] Blood
 - [2] Tissues
 - (e) Nonprotein nitrogen
 - (2) Increase in size of liver

2 Units

- a Normal, plateaued rat—the amount of any preparation that will produce a gain of 40 Gm in total body weight with 17 injections by 20 days^{2 5}

- b Hypophysectomized rat—the amount of any preparation that will produce a gain of 10 Gm in total body weight with 9 injections by 10 days

C GONADOTROPINS

- 1 Follicle stimulating hormone (substance must be free of luteinizing hormone)

a Methods

- (1) Weight gain in
 - (a) Ovaries (hypophysectomized or immature rats)^{1 4 5}
 - (b) Uterus (normal mice)⁸
 - (c) Testes (hypophysectomized rats)⁴
- (2) Estrus vaginal smears¹¹
- (3) Histologic examination for beginning follicular development (hypophysectomized rats)^{6 7}

b Units

- (1) Rat—minimal amount of unknown given subcutaneously, one third the total amount injected daily over a 3 day period into hypophysectomized female rats (26 to 28 days old at operation and 6 to 8 days postoperatively) which causes resumption of follicular growth within 72 hrs after the last dose^{6 7}
- (2) Mouse—the smallest amount of preparation which, given subcutaneously to 5 or more mice (21 to 23 days old) in one third portions at 24 hr intervals, produces from 100 to 150 per cent increase in uterine weight by 72 hrs⁸
- 2 Luteinizing hormone (or interstitial cell stimulating hormone)
 - a Methods
 - (1) Weight gain in
 - (a) Ovaries (normal, immature hypophysectomized rats)^{1 4}
 - (b) Seminal vesicle (normal immature rats)^{1 4}
 - (c) Testes (normal immature pigeons or 1 day old chicks)¹⁰
 - (d) Ventral lobe of the prostate (hypophysectomized male rats)⁻⁴

- (f) Heat labile in oxygen (absence or presence)
- (g) Inactivated by
- {1} Cysteine
 - {2} Ketene
 - {3} Benzoyl chloride
 - {4} Nitrous acid
 - {5} Trypsin
 - {6} Pepsin
- (h) Protein color reactions
- e Adrenocorticotrophic hormone (sheep and swine pituitary glands)^{5 10 11}
- (1) Molecular weight 20 000
 - (2) Isoelectric point 4.7
 - (3) Content
- | | PER CENT |
|------------------|-------------|
| (a) Carbon | 46.35 50.64 |
| (b) Nitrogen | 15.65 15.47 |
| (c) Cystine | 7.19 |
| (d) Hydrogen | 5.89 6.23 |
| (e) Sulfur | 2.30-2.33 |
| (f) Methionine | 1.93 |
| (g) Carbohydrate | 0 |
| (h) Phosphorus | 0 |
- (4) Properties
- (a) Soluble in water
 - (b) Stable at 100° C unlike all other pituitary hormones
 - (c) Stable toward pepsin
 - (d) Inactivated by trypsin
- (5) Essential groups for biologic action
- (a) Amino
 - (b) Phenolic hydroxyl
- f Lactogenic hormone (sheep and ovine pituitary glands)^{11 12 13 14}
- (1) Molecular weight 25 000 to 32 000
 - (2) Isoelectric point 5.73
 - (3) Content
- | | PER CENT |
|-------------------|----------|
| (a) Carbon | 51.81 |
| (b) Nitrogen | 16.5 |
| (c) Glutamic acid | 12.3 |
| (d) Arginine | 8.3 |
| (e) Hydrogen | 6.81 |
| (f) Tyrosine | 4.5 5.7 |
| (g) Methionine | 4.3 |
| (h) Cystine | 3.0-3.4 |
| (i) Tryptophan | 1.2 2.5 |
| (j) Sulfur | 1.8 2.0 |
| (k) Phosphorus | 0 |

- (4) Properties
- (a) Destroyed by
 - {1} Pepsin
 - {2} Trypsin
 - (b) Soluble in absolute methyl or ethyl alcohol
 - (c) Insoluble in water
 - (d) Thermolabile (altered by various factors)
 - (e) Inactivated by
 - {1} Mild hydrolysis
 - {2} Reagents affecting amino acids or disulfide groups
 - {3} Iodine
 - (f) Treatment with urea increased the viscosity of solutions with loss of potency
- B INTERMEDIATE LOBE⁵
- 1 Specific metabolic factor (?)
- a Formula is unknown
 - b Properties
 - (1) Destroyed by prolonged treatment with trypsin
 - (2) Resistant to
 - (a) Alkalis
 - (b) Peptic digestion
 - (c) Heat
 - (3) Thermostable in aqueous solution
- 2 Melanophore stimulating factor (?)
- a Formula not determined
 - b Constituents that are known
 - (1) Tyrosine
 - (2) Arginine
 - (3) Cystine
 - c Properties
 - (1) Destroyed by prolonged boiling with mineral acids
 - (2) Stable to
 - (a) Boiling alkalis (therefore not identical with vasopressin or oxytocin)
 - (b) Dilute acetic acid
- C POSTERIOR LOBE^{5 23 30}
- 1 'Mother molecule'
- a Ratio of three hormones 1:1:1
 - b Molecular weight 30,000
 - c Isoelectric point 4.8
 - d Contents which have been determined
 - (1) Exact formula is unknown for any of the principles

- b Redistribution of cortical lipids in adrenals of hypophysectomized, mature female rats (repair test)^{6 13}

■ Cholesterol or ascorbic acid content in adrenals of

(1) Rats

(a) Normal immature (24 days old)¹⁰

(b) Hypophysectomized — one adrenal removed and its ascorbic acid content compared with remaining one after intravenous injections of hormonal preparation¹¹

(2) Guinea pigs (300 to 450 Gm)¹¹

- d Determination of mitoses in the cells of adrenal cortex of guinea pigs³

2 Units

a Repair—total dose in milligrams necessary to start redistribution of lipids and an increase in width of the adrenal cortical in female rats, 26 to 28 days old at time of hypophysectomy and 14 days postoperatively, given 4 daily intraperitoneal injections¹³

b Maintenance—daily dose in milligrams required to maintain preoperative adrenal weight for 15 days in hypophysectomized male rat at 40 days of age⁶

c Sudanophobic—the smallest amount of substance which is injected twice daily for 8 days into hypophysectomized rats (weighing from 80 to 120 Gm from 10 to 20 days postoperatively after one adrenal is removed and stained with sudan and examined for development of the Sudanophobic zone) which will restore the Sudanophobic zone to normal (compared with previously removed adrenal)⁹

d Ascorbic acid—the substance is injected intraperitoneally thrice daily for 3 days (4 mg/100 Gm of body weight) into 24 day old rats or guinea pigs (300 to 450 Gm), then the ascorbic acid content of the adrenals is determined and compared with a standard¹⁰

F LACTOGENIC HORMONE

- 1 Riddle Bates (preferred method)^{1 4}
6 12

a Method

(1) Minimal amounts of unknown are injected intramuscularly in to pigeons

(2) Weight of excised crop gland is determined

b Unit—the smallest concentration of substance given intramuscularly daily for 4 days into 2 to 3 month old pigeons which will cause within 96 hrs after the first injections an increase in the weight of their crop glands

2 Lyons⁵

a Method

(1) Crop glands of pigeons are injected intradermally for 4 days with the unknown extract

(2) Pigeons are killed on the fifth day

(3) Sacs are dissected and examined against the light with naked eye

b Unit—the amount required for a majority of 5 injected birds to show positive crop responses

3 Reece Turner¹¹

a Method

(1) Unknown preparation is injected intradermally over the crop gland area of pigeons

(2) Degree of response is determined

b Unit—the amount of hormone which when injected intradermally over the crop gland for 4 days, will cause an area of proliferation there about the size of a nickel

4 Minimum micro unit (Missouri)

a Method

(1) Intradermal injections of unknown are given over the crop sac

(2) Glands are examined and rated by viewing them by transmitted light

b Unit—the amount of hormone injected intradermally over the crop gland of 20 common pigeons which will elicit a minimal response in 50 ± 11 per cent of the pigeons

- (2) Repair in ovarian interstitial tissue (hypophysectomized rats)
5 9

- (3) Melanin reaction in feathers of African weaver finches¹¹

b Units

- (1) Ovarian weight—minimal amount given intraperitoneally one third the amount injected daily for 3 days, into hypophysectomized rats (26 to 28 days old at operation and 6 to 8 days postoperatively) which will cause repair of deficient interstitial cell tissue of ovary with in 72 hrs after the last dose^{1 4}
- (2) Ventral prostate weight—the amount given subcutaneously is 1 cc (representing $\frac{1}{4}$ of total dose) once daily for 4 days into hypophysectomized immature male rats (21 to 22 days of age at operation the injections start 2 days postoperatively) the autopsy is performed on the fifth day and the increase in weight of the ventral prostate is determined⁴

D THYROTROPIC HORMONE

- 1 Methods—thyroid gland has been used as an index of potency

- a The changes are determined by

- (1) Weight— $\text{increase}^{1-6 \ 10 \ 11 \ 16 \ 20}$
22 23 3
- (2) Iodine content— $\text{decrease}^{10 \ 16 \ 27}$
- (3) Cytologic alterations^{7 \ 11 \ 12, \ 13}
15 16 19 23 26 28
- (4) Combinations of (1) and (3)

- b The following normal immature animals are used

- (1) Guinea pigs^{6 \ 10 \ 13 \ 16 \ 17 \ 9 \ 23 \ 7}
22 23 27
- (2) Chicks (1 to 3 days old)^{6 \ 7 \ 9 \ 11}
22 23 27
- (3) Rats (may be hypophysectomized)^{8 \ 10 \ 1}
- (4) Tadpoles (axolotls)^{10 \ 1}

- 2 Units (each varies with the type of test)

- a International standard—1 unit is equivalent to 250 micrograms of the preparation²¹

b Guinea pig

- (1) Junkmann Schoeller¹⁵

- (a) One—the least amount given daily which produces unmistakable alterations in the thyroid cells over a 4 day period, i.e., beginning cuboid to cylindrical epithelium and diminishing colloid in 2 infantile guinea pigs (100 to 150 Gm)

- (b) Two—daily requirement that results in well marked changes beyond the border line

- (c) Three—daily quantity that produces practically no colloid and the follicles have very small lumens

- (2) Rowland Parkes—the total amount injected daily for 5 days into 1 700 Gm female guinea pig which will cause the thyroid to double its weight or attain a weight of 60 mg²⁰

- (3) Bergmann Turner—the total amount of hormone injected subcutaneously for 5 days which will produce a 50 per cent mean weight increase in the thyroids of 10 male animals (average weight 115 ± 15 Gm)⁶

c Chick⁹

- (1) Total amount of hormone injected subcutaneously daily over a 4 day period which will cause a mean increase in weight of 20 per cent (or 50% in males) in the thyroids of 20 chicks (average weight of 55 ± 10 Gm)

- (2) This unit is about one fourth of the guinea pig unit

E ADRENOCORTICOTROPIC HORMONE

1 Methods

- a Adrenal gland weight increase determined in

- (1) Rats^{7 \ 8 \ 1}

- (a) Normal 4 or 21 days old

- (b) Hypophysectomized (maintenance test)^{1 \ 12 \ 13}

- (c) Hypophysectomized and unilateral adrenalectomy^{4 \ 18 \ 13}

- (2) Chicks 2 days old

J SPECIFIC METABOLIC PRINCIPLE¹

1 Method

- a A definite amount of preparation is given subcutaneously to the animal
- b Certain precautions are necessary in preparing the material (vasopressin, thyrotropic hormone, dosage, and so forth must be considered)
- c The following animals may be used
 - (1) Rabbits (most sensitive)
 - (2) Rats
 - (3) Guinea pigs
- d Respiratory quotient decreases at a definite interval following the injection

2 Unit (rabbit)

- a The minimal amount given subcutaneously to a 2 Kg rabbit which will cause the maximal metabolic stimulation around the third hour
- b One cc produced a
 - (1) Twenty per cent increase of metabolism
 - (2) Reduction of 0.12 in respiratory quotient

K MELANOPHORE STIMULATING FACTOR

1 Frogs (hypophysectomized)

a Methods

- (1) Activity is determined by the time required for the melanophores to return to full contraction after injection of the preparation^{1 6 8 12 13}
- (a) Comparison of an unknown with a known amount of hormones
- (b) Difficult test
- (2) Perfusion of frog's legs^{1 7 13}
 - (a) Frog is pithed
 - (b) Ringer's solution is used until melanophores are contracted
 - (c) A given amount of unknown extract is added to the solution after two of the frog's legs are tied off as controls
 - (d) Perfusion
 - (e) The color change is determined within a definite time
 - (f) The threshold of concentration is found for the solution by several trials
 - (g) Difficult test

(3) Perfusion of frog's skin [based on methods (1) and (2)]⁶

b Unit—not defined

2 Toads (hypophysectomized)¹¹

a Method

(1) Same as for frogs [method 1]

(2) Modified test

- (a) Extract is injected into dorsal lymph sac of toad which is fully pale (animal is kept on white background in order to lose its pigment)
- (b) About 10 per cent accuracy, results are not influenced by other posterior lobe principles

b Unit (international)—melanophore activity is that amount in 0.5 mg of international standard posterior lobe powder

3 Fish

■ Minnow (*Phoxinus phoxinus*)

(1) Method

- (a) The amount of hormone producing a red area (erythrophore response) of 4 to 9 sq mm at the attachment of the fin is determined^{14 15}
- (b) Animal cannot be used during breeding season
- (c) Nonspecific test
- (d) Modification of procedure degree of response in an isolated fin or scales immersed in solution may be measured microscopically^{3 11}

(2) Unit—this is based on the size of the red color reaction

b Atlantic minnow (*Fundulus heteroclitus*)

- (1) Method—melanophore expansion at the denervated caudal area test is rapid and accurate
- (2) Unit—the amount of hormone producing a darkening of the denervated caudal area in 25 per cent of minnows within 30 min after intraperitoneal injection

4 Lizard (*Anolis*)¹⁰

a Method

- (1) Hypophysectomized animal injected intraperitoneally with solution

5 McShan Turner^{9 10}

- a Method—breast muscles of pigeons are injected with unknown material
- b Unit—the amount of hormone injected during 4 days which will cause a minimum proliferation of crop glands of 50 ± 11 per cent of 20 common pigeons

6 Gardner Turner (rabbit unit)³

- a Method
- (1) Pseudopregnancy is induced in rabbits by an intravenous injection of chorionic gonadotropic substances (50 rat units)
 - (2) On fourteenth day, mammary glands are checked for development
 - (3) For next 6 days lactogenic preparation is injected
 - (4) On seventh day, the degree of enlargement and the secretion of mammary glands are rated
 - (5) Rating—mere duct lactation (one plus) to lactation observed in parturient animals (four plus)
- b Unit—the response to an average plus three rating showing that entire gland is filled with milk in at least 6 animals (definite rating basis is established)

7 Guinea pig (nulliparous) may be used by determining lactation response^{4 7}8 International unit³

- a Method
- (1) Administration of unknown by either local or systemic route
 - (2) Crop gland growth determined in pigeons and doves
- b Unit—1 unit is the amount of activity contained within 1 mg (100 gamma) of standard preparation

9 Relationship of units

	Units/Gm of initial extract*	Relation to McShan Turner unit
a Riddle Bates	3 750	1 5
b Lyons macro units	1 875	0 75
c Reece Turner	55 556	22 2
d Minimum micro method	444 445	177 8

Units/Gm
of initial
extract*

Relation
to
McShan
Turner
unit

e McShan Turner	2,500	1 0
f Gardner Turner	9 2	0 0037

* Purified hormone was not used

G MAMMOGEN I (?)^{1 4}

- 1 Method—development of mammary ducts in male albino mice (normal rudimentary glands do not respond to gonadotropic hormones)
- 2 Unit—total amount of tissue or extract, given subcutaneously once daily for 6 days, which produces definite signs of duct development in one or more glands of 50 ± 10 per cent of 10 male albino mice weighing 10 to 25 Gm the glands are removed and analyzed on the seventh day

H MAMMOGEN II (?)¹

- 1 Method
 - a Lobule alveolar development of mammary glands in ovariectomized, virgin mice
 - b Results compared with glands from mice that are from 4 to 8 days pregnant
- 2 Unit—the amount required per mouse, injected subcutaneously for 10 days, to obtain definite lobule alveolar development in 50 ± 10 per cent or more castrate nulliparous female mice (weight 12 to 18 Gm)

I FAT METABOLISM HORMONE (?)¹⁻³

- 1 Methods
 - a Guinea pig (female)—depression of fat plasma is determined after injection of pituitary extract
 - b Rabbit—reduction of fat (blood) around 36 per cent in 6 to 8 hrs with a single injection of anterior pituitary extract³
 - c Mouse—fatty infiltration of liver
- 2 Unit—minimum amount of extract which will depress plasma fat of at least 6 guinea pigs on the average of 30 to 50 per cent of the normal (60 mg %)

IX PATHOLOGY

A GROSS

TABLE 6 SURGICAL PATHOLOGY OF COMMON
TUMORS IN OR ADJACENT TO SELLA
TURCICA (HORRAX¹⁰)

	SIZE	APPEARANCE	CAPSULE	LOCATION	POSSIBLE EXTENSIONS
Chromophil	From almost microscopic to large*	Rounded smooth reddish gray†	Thin few small blood vessels on surface	Intrasellar central or may be largely unilateral	May push through diaphragm displacing one or both optic nerves upward or to sides bury deep into sphenoid sinus or extend to frontal lobe and third ventricle
Chromophobe	1 cm in diameter to large	Rounded smooth reddish gray	Thin few small blood vessels on surface‡	Intrasellar	May push through diaphragm displacing one or both optic nerves upward or to sides bury deep into sphenoid sinus or extend to frontal lobe and third ventricle Greater tendency to displace both optic nerves than in chromophil
Cranio pharyngioma	2 to 3 cm to very large	Pale or yellowish translucent bulging	Thin or very dense and thick	Usually above sella but may be intrasellar	May extend in any direction occasionally back as far as pons may surround sella
Meningioma	2 to 3 cm to very large	Granular grayish red	Resistant and thin	Above and attached to tuberculum sellae	Usually localized above site of origin
Glioma	1 cm to very large	Grayish white	Little or none present	In one or both optic nerves or chiasm	Forward to one or both orbits or back to chiasm
Epidermoid	2 to 3 cm to very large	Mother of pearl	Fine (one layer of epithelium)	Midline under optic nerves	May extend back along base of skull
Aneurysm of internal carotid	1 cm to large	Smooth color as that of large artery may not pulsate	Fibrous covering as in all blood vessels	Adjacent to sella	Expands against sella

* Large can be considered size of hen's egg

† The reddish gray color approaches that of a large artery

‡ When degenerated and/or cystic appearance changes

II MICROSCOPIC INCLUDING HISTOPHYSIOLOGY

1 Introduction

- A great variety of lesions have been found in the hypophysis
- The following summary does not attempt to correlate the pathology with clinical states
- Animal experiments included here may demonstrate similar effects in humans

2 Atrophy¹¹

- Variable changes
- Eosinophils—absent
- Lymphocytes—present
- Fibrosis
- Hyaline degeneration
- Causes
 - (1) Arteriosclerosis
 - (2) Embolus
 - (3) Inanition
 - (4) Trauma

(2) Degree of pigment dispersion is determined

(3) Color changes fall into a definite stage, which is given a numerical value

(4) Better test than others

b Unit—weight of pituitary powder which, injected into these animals after being in the form of neutralized sodium hydroxide extract produces a color response

L VASOPRESSIN

1 Methods

a Blood pressure in decerebrate animals^{3 4 7}

b Solution to be assayed is injected into vein of anesthetized dog or cat^{1 6}

(1) Blood pressure increase is compared with a known standard

(2) Most commonly used test

c Smooth muscle (ileum) contractions of guinea pig are evaluated⁸

2 Unit

a One unit represents the activity that is exhibited by 0.5 mg of U S P standard powdered pituitary (based on pressor activity in anesthetized dog or cat)

b One milligram of international standard powder represents about 7 mg of fresh posterior lobe (ov)

M OXYTOCIN

1 Methods

a Guinea pig (immature) (official method)

(1) Muscular response of isolated uterus immersed in modified Locke's solution is compared with a standard preparation^{1 2}

(2) Other animals may be used

(a) Sheep (less sensitive)^{9 11}

(b) Puerperal cat⁷

(c) Rabbit¹³

b Chickens or roosters—by study of blood pressure effects¹⁰⁻¹²

2 Unit

a One unit represents the activity of 0.5 mg of standard powder (U S P)

b Preparation is adjusted to an activity of 10 units/cc of solution

N ANTIDIURETIC FACTOR

1 Methods

a Water diuresis inhibition^{2 3 8}

(1) Unanesthetized animal (rats, mice)

(a) The amount of extract required to delay the excretion of administered water is determined

(b) Water is given by either stomach tube or intraperitoneal injections

(c) Animals are hydrated by 5 per cent of body weight of water^{4 9 10}

(d) A curve is plotted of the urine elimination at definite intervals determined by the maximum time of output and also the time required for excretion of half the administered water^{2 3}

(e) Findings are compared with the controls for calculation of results^{9 11 12}

(f) Anti diuretic effect is inversely proportional to the water load

(g) Preferred test

(2) Dogs with bladder fistulas may be used¹⁰

(3) Animals (rats rabbits) are rendered diuretic by water or alcohol, and the minute anti diuretic action of pitressin can be detected^{7 11}

b Changes in body water (frogs)¹

c Chloruretic effect of posterior lobe preparations (rats)

d Diabetes insipidus (dogs female)⁶

(1) Unknown material given intravenously

(2) Ratio of urinary creatinine plasma creatinine determined

(3) Response is compared with standards

(4) Amounts of antidiuretic material is detected readily in

(a) Tissue

(b) Blood

(c) Urine

2 Unit—not well defined

- (4) Malignant type of tumor does not retain alveolarlike arrangement (see Fig 23)
- (5) Adenoma structure may not be present, but rather a diffuse or nodular hyperplasia
- c Basophilic—see 11 \ B 1
- d Mixed
- (1) Cells may be combination of
- Acidophils
 - Chromophobes
 - Nondescript type
- (2) Little resemblance to normal arrangement
- (3) Groups of irregular masses with sharp boundaries
- e Craniopharyngioma^{16 81}
- (1) It is called
- Craniopharyngeal duct tumor
 - Rathke's pouch tumor
 - Suprasellar cyst
 - Adamantinoma
- (2) Solid
- Epithelial nests are
 - Made of multiple projections
 - Lined by cylindrical cells arranged in concentric circles
 - Surrounded by loose connective tissue
 - Various changes may develop
 - Necrosis
 - Small horny bodies
 - Tiny pseudocystic areas
 - Calcification
 - True bone tissue from sclerotic hyaline fibrosis and may be mistaken for teratoma
 - Malignant degeneration occasionally (prickly and smooth cells)
- (3) Cystic—true type may be lined with
- Fibrous tissue
 - Papillary outgrowths in which degenerative changes take place
- f Miscellaneous
- Sarcoma
 - Lymphosarcoma
 - Fibroma
 - Angioma
 - Teratoma
 - Psamomma
 - Lipoma
 - Cholesteatoma (from cranio pharyngioma or epidermoid carcinoma)
 - Carcinoma^{8 16 20}
 - Metastatic lesions from
 - Brain
 - Breast
 - Bronchus
 - Prostate
 - Cysticercus
 - Echinococcus
- 13 Hyperplasia (general) has been noted in
- Gigantism
 - Acromegaly
 - Myxedema (see below)
 - Hyperthyroidism (see below)
 - Castration (physiologic or surgical)
 - Pregnancy
 - Hypertension (?)
- 14 Myxedema or thyroidectomy^{1 73 39 56 71 79 80-8 90 93 99 100}
- Acidophils
 - Greater decrease than in castration
 - Colloid content increased^{7 10}
 - Basophils—increased
 - Findings similar to those with castration, but may be differentiated by special staining methods
 - Vacuolization usually found
 - Pituitary size—increased^{1 6 31 5 53 55 61 68 73 74}
 - Changes are almost identical with those of thyroidectomized animals^{1 76}
- 15 Hyperthyroidism^{56 79 8}
- No specific change in normal pituitary cytology has been established
 - Acidophils
 - Numbers—decrease but do not disappear
 - Granules—brilliant
 - Golgi apparatus—hypertrophied
 - Mitochondria—enlarge

- 3 Pressure atrophy⁴⁴
 - a Cells shriveled, may not be recognized
 - b Colloid—scant
 - c Fat deposits
 - d Edema due to hydrocephalus
- 4 Hypoplasia
 - a Pituitary size—decreased
 - b Chromophobes (small)—predominant
 - c Eosinophils—few, if any (dwarfism)⁴⁵
 - d Causes same as for atrophy (see above)
- 5 Regeneration of tissue may occur following postpartum necrosis (Sheehan's disease)⁴¹
- 6 Necrosis^{41 42}
 - a Characteristic findings for any necrotic tissue
 - b Causes
 - (1) Embolus
 - (2) Thrombosis
 - (3) Infection
 - (4) Tuberculosis
 - (5) Syphilis
 - (6) Tumor
 - (7) Eclampsia
 - (8) Miscellaneous
- 7 Other degenerative changes
 - a Types
 - (1) Hyaline
 - (2) Amyloid
 - (3) Hemosiderin (hemochromatosis)
 - (4) Lipoid
 - (5) Calcium
 - (6) Cholesterol deposits
 - (7) Colloid accumulations within follicularlike structures
 - (8) Hydropic
 - (9) Fatty
 - b Causes are any listed under B 2 to 6 above
- 8 Congestive hyperemia⁴⁴
 - a Blood vessels often are
 - (1) Enlarged
 - (2) Increased in number
 - b Causes
 - (1) Congenital heart anomalies
 - (2) Congestive heart failure
 - (3) Polycythemia
 - (4) Emphysema
- 9 Hemorrhage⁴⁴
 - a Extravasation of blood into surrounding tissues
 - b Causes
 - (1) Skull fracture
 - (2) Necrosis
 - (3) Sepsis
 - (4) Miscellaneous
- 10 Infarct^{44 46}
 - a Large or small ones may be found
 - b Causes
 - (1) Endarteritis which may be
 - (a) Embolic
 - (b) Bacteremic
 - (c) Thrombotic
 - (d) Arteriosclerotic
 - (2) Postpartum hemorrhage, if sufficiently severe, produces an 'anemic infarct'
- 11 Specific diseases (rare)⁴⁴
 - a Syphilis
 - b Tuberculosis⁴⁷
 - c Anthrax
 - d Leukemia
- 12 Tumors
 - a Chromophobic⁴⁴
 - (1) Embryonic type of cell common
 - (2) Acidophils—rarely
 - (3) Cytoplasm—pale often vacuolated
 - (4) Nuclei—not much larger than endothelial cell nuclei
 - (5) Granules—absent
 - (6) Nuclei
 - (a) Round
 - (b) Irregular
 - (7) Alveolar arrangement of cells may occur
 - (8) Colloid is present in
 - (a) Cells
 - (b) Alveoli
 - (9) Connective tissue variable
 - (10) Tumor may be
 - (a) Solid, tough, like muscle
 - (b) Cystic occasionally
 - b Acidophilic⁴²
 - (1) Cells—arranged in strands and alveolarlike structure
 - (2) Cytoplasm—eosinophilic
 - (3) Nuclei
 - (a) Ovoid or round
 - (b) Sharply stained
 - (c) Two times larger than endothelial cell

- i Thymus extract—acidophils are increased (?)⁴
- j Antigonadotropins⁸³
 - (1) Chromophobes are rarely found in typical areas
 - (2) Acidophilic stain modified
 - (3) Basophils show
 - (a) Hyalinization
 - (b) Vacuolation
 - (c) Replacement by large, sparsely granulated cells, rich in mitochondria
 - (4) Pituitary
 - (a) Hyperemic
 - (b) Edematous
- k Goitrogenic agents produce same effects as with thyroidectomy⁸
 - (1) Sulfaguanidine⁵
 - (2) Thiouracil⁷²
 - (3) Promizole³⁶
- l Vitamins
 - (1) A and C (rabbits)³
 - (a) Acidophils—increased
 - (b) Basophils—increased slightly
 - (2) B deficiency (humans)⁴
 - (a) Pars glandularis may have necrotic areas
 - (b) Adenomalike arrangements of oxyphils and basophils
 - (3) E deficiency—castration changes may be found (rats)⁶⁰
 - (4) D—oxyphils affected (dogs)⁶⁵
- c Absent
- d Hypertrophy
- e Hyperplasia
- f Abnormal location by extension
- g Aberrant
- h Adenomatous
- i Cyst
- j Aneurysm
- k Malignant
 - (1) Primary
 - (2) Secondary
- l Acute inflammation
 - (1) Suppurative
 - (2) Nonsuppurative
- m Chronic inflammation
 - (1) Suppurative
 - (2) Nonsuppurative
- n Hemorrhage
- o Infarct
- p Thrombosis
- q Necrosis
- r Other degenerative changes
- s Compression
- t Metastases
- u Postoperative remnants
- v Recurrent
- w Calcification

3 Hormonal

- Present
 - (1) Normal
 - (2) Normal without end organ response
 - (3) Hyposecretion
 - (4) Hypersecretion
 - (5) Premature
- b Past
 - (1) Normal
 - (2) Normal without end organ response
 - (3) Hyposecretion
 - (4) Hypersecretion
 - (5) Premature

X CLASSIFICATIONS

A COMPREHENSIVE LIST OF CHIEF FACTORS IN ENDOCRINE DISEASES

- 1 Etiologic
 - a Congenital
 - b Hereditary
 - c Nutritional (including vitamins)
 - d Chemical
 - e Infection
 - f Radiation
 - g Surgical
 - h Hormonal
 - i Malignancy
 - j Neuropsychic (via hypothalamus)
 - k Unknown
 - l All others
- 2 Gross anatomic and pathologic
 - a Normal
 - b Atrophy
- 4 Histologic
 - a Normal
 - b Hypoplasia
 - c Atrophy
 - d Hypertrophy
 - e Hyperplasia
 - f Adenomatous
 - g Hemorrhage
 - h Infarct
 - i Suppurative
 - j Nonsuppurative

- c Basophils increase in
 - (1) Size
 - (2) Number
 - (3) Vacuolization
- d Pituitary may decrease in size^{19 24}
- 16 Addison's disease^{5 12, 13 4 47 50 57}
 - a Acidophils—decreased
 - b Basophils—decreased (anterior and posterior lobes)
 - c Chromophobes—increased
- 17 Hyperadrenocorticalism—findings similar to basophilism (see 11 \ B 1)
- 18 Pancreatectomy—basophils are²⁷
 - a Enlarged markedly
 - b Degranulated
 - c Vacuolated
 - d Similar to hyalinized Crooke cells (see 11 \ B 1)
- 19 Hypertension^{4 13 15 16 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101}
 - a Clinical entities in which basophilic changes may be significant are
 - (1) Eclampsia
 - (2) Nephritis
 - (3) Nephrosclerosis (benign or malignant)
 - (4) Essential type
 - b Basophils increase in
 - (1) Posterior lobe with hypertension
 - (2) Anterior lobe with diseases of the kidneys
 - c Significance of the pituitary cytology found in these conditions is still unsettled
- 20 Chorionepithelioma and teratoma^{1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101}
 - a Acidophils—decreased
 - b Changes similar to those of pregnancy
- 21 Carcinoma of breast—no significant changes¹¹³
- 22 Effects due to administration of different preparations (Ordinary laboratory animals were used results have been controversial due to many variable factors i.e. dosage age type of animal and so forth)
 - a Growth hormone⁴
 - (1) Chromophobes—increase
 - (2) Acidophils—decrease
 - (3) Basophils—no change
 - (4) Pituitary size—normal
 - b Adrenocorticotrophic hormone⁴⁴
 - (1) Basophils—increase in size
 - (2) Pituitary weight—decreased
 - c Parathyroid hormone—acidophils are decreased (opposite with parathyroidectomy)⁴
 - d Male sex hormone (testes extracts or androgenic preparations)
 - (1) Cytologic effects are similar to administered estrogens^{11 34 35 43 49 51 53 75 90-95}
 - (2) Pituitary weight is not altered in normal or spayed rats^{43 90-95}
 - e Estrogens^{10 17 23 24 103}
 - (1) Chromophobes
 - (a) Number—increased¹⁰¹
 - (b) Mitotic activity—remains unchanged
 - (2) Acidophils
 - (a) Number—decreased¹⁰¹
 - (b) Mitotic activity—enhanced
 - (c) Golgi apparatus—hyperthrophied
 - (d) Hyperplasia⁹⁵
 - (3) Basophils
 - (a) Number—decreased
 - (b) Mitotic activity—unaffected
 - (c) Golgi apparatus—very large
 - (d) Mitochondria—numerous
 - (e) Degranulation occurs^{21 51 6 67 81 90}
 - (4) Other demonstrated changes
 - (a) Pituitary gland shows great hypertrophy and weight increase^{9 13 78 94 95 102}
 - (b) Eosinophilic hyperplasia produced in humans by prolonged and large doses of estradiol¹⁰¹
 - (c) Reversion to normal pituitary cytology following ovariectomy^{11 38 50 53 73 80}
 - f Progesterone
 - (1) Pituitary weight may increase²⁷
 - (2) Castration effects found in pituitary remain the same²⁷
 - g Castrate urine, placental or fetal extracts change chromophobe cells
 - (1) Number—increased
 - (2) Degranulation
 - h Insulin injections (repeated)⁴
 - (1) Results—inconsistent
 - (2) Acidophils—involved probably

- b Midpuberal
 - c Postpuberal
 - (1) Simmonds' disease
 - (2) Sheehan's disease
 - 2 Selective or predominate deficiencies
 - a Hypogonadotropic hypogonadism
 - (1) Prepuberal
 - (2) Midpuberal
 - (3) Postpuberal
 - b Pituitary myxedema
 - c Pituitary adrenocortical insufficiency
 - d Prepuberal growth and gonadotropic deficiencies (transient)
 - 3 Diabetes insipidus
 - 4 Gigantism
 - 5 Acromegalic gigantism
 - 6 Acromegaly
 - 7 Cushing's syndrome (basophilism)
 - 8 Mixed syndromes
 - a Pituitary dwarfism followed by gigantism
 - b Fugitive acromegaly and hypopituitarism
- D TUMORS**
- 1 Adenoma
 - a Chromophobic
 - b Eosinophilic
 - c Basophilic
 - d Mixed
 - 2 Craniopharyngioma
 - 3 Miscellaneous
- XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION**
- A INTRODUCTION**
- 1 Separate clinical entities do not exist for each hormone although theoretically possible adequate evidence is not available
 - 2 The reader is referred to predominant or selective hypofunction under
 - a Hypopituitarism—see 6, 7
 - b Hypogonadism—see 47 XVI B 2 61 II E 3, 4 65 VIII
- II GROWTH HORMONE**—Growth and somatic development are retarded
- C GONADOTROPIC HORMONES**
- 1 Gonadal hypoplasia
 - a Amenorrhea
 - b Aspermatogenesis
 - c Sexual function lost
 - 2 Symptoms as in
 - a Hypogonadotropic hypogonadism
 - b Panhypopituitarism
- D THYROTROPIC HORMONE**
- 1 Thyroid hypoplasia—low basal metabolic rate as in hypopituitarism
 - 2 Idiopathic myxedema—possible, but unproved
- E ADRENOCORTICOTROPIC HORMONE**
- 1 Adrenal hypoplasia
 - 2 Symptoms as in hypopituitarism
 - a Hypotension
 - b Alopecia of body and sexual hair
 - c Asthenia
 - d Hypoglycemia
 - e Anemia
- F LACTOGENIC HORMONE**—Agalorrhea
- G PARATHYROTROPIC HORMONE**—Idiopathic atrophy of parathyroids, if existence of hormone is proved
- H POSTERIOR LOBE HORMONES**—Polyuria and polydipsia as in diabetes insipidus but other factors may exert an influence (see 8 XI B 2, 3)
- XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION**
- A INTRODUCTION**
- 1 Attempts to assign a role to each hormone in cases of hyperfunction is not yet possible and perhaps never will be, since isolated hormones do not necessarily represent the products secreted by the gland
 - 2 However, certain effects such as those produced by growth and adrenocorticotrophic hormones have fairly typical clinical signs
- II GROWTH HORMONE**—Skeletal and tissue overgrowth as in gigantism and acromegaly
- C GONADOTROPIC HORMONES**
- 1 Hyperplasia and hyperfunction of Leydig cells as occasionally found in acromegaly
 - 2 Result of castration, male or female
 - 3 Relationship to climacteric symptoms is not definitely established
- D THYROTROPIC HORMONE**
- 1 Thyroid hyperplasia or hypertrophy
 - a Graves's disease with or without exophthalmos, but proof is lacking

- k. Carcinoma
- l. Degenerative and infiltrative changes
 - (1) Hyaline
 - (2) Fatty
 - (3) Fibrotic
 - (4) Pigmentary
 - (5) Lymphocytic
 - (6) Leukemic
 - (7) Malignant
 - (8) Hydropic
 - (9) Others

m. Regeneration

5 Therapeutic

a. Present

- (1) None
- (2) Surgical
- (3) Radiation
- (4) Drugs
- (5) Hormonal
- (6) Dietary

b. Past

- (1) None
- (2) Surgical
- (3) Radiation
- (4) Drugs
- (5) Hormonal
- (6) Dietary

B HORMONAL

1 Hyposecretion

a. Growth hormone

- (1) Prepuberal
 - (a) Pituitary dwarfism
 - (b) Cretinism (see 24 XI)
- (2) Midpuberal to, puberal arrest

b. Gonadotropic hormones

- (1) Follicle-stimulating and luteinizing hormones
 - (a) All panhypopituitary cases
 - (b) Selective "FSH" deficiency (eunuchoidism or secondary amenorrhea)
- (2) Follicle stimulating hormone—no clinical syndrome known
- (3) Luteinizing hormone
 - (a) Pubescent males with follicle stimulating hormone which is normal or increased
 - (b) Failure of ovulation
 - (c) Menstruation
 - [1] Normal
 - [2] Amenorrhea
 - [3] Excessive bleeding

c. Thyrotropic hormone

- (1) All panhypopituitary cases
- (2) Selective predominant deficiency in hypopituitarism
- (3) Idiopathic myxedema (possible)

d. Adrenocorticotrophic hormone

- (1) All panhypopituitary cases
- (2) Selective predominant deficiency in panhypopituitarism

e. Posterior lobe hormones—diabetes insipidus, anterior lobe should be functioning normally

2 Hypersecretion

a. Growth hormone

- (1) Prepuberal—gigantism
- (2) Midpuberal—acromegalic gigantism
- (3) Postpuberal—acromegaly

b. Gonadotropic hormones

- (1) Follicle stimulating and luteinizing hormones
 - (a) Acromegaly possibly
 - (b) Castration any age
 - (c) Natural climacteric
 - (d) Ovarian agenesis
- (2) Follicle stimulating hormone
 - (a) Impubescent state with LH deficiency
 - (b) Tubular disease
 - (c) Castration
 - (d) Natural climacteric
- (3) Luteinizing hormone—tubular disease with inhibin deficiency

c. Thyrotropic hormone

- (1) Possible in 2a above
- (2) After thyroidectomy
- (3) Primary myxedema
- (4) Postulated in thyroid hyperfunction
- (5) Exophthalmic syndrome

d. Adrenocorticotrophic hormone

- (1) Predominance of 'S' hormones, i.e. Cushing's syndrome
- (2) Predominance of 'N' hormone
 - (a) Adrenogenital syndrome
 - (b) Pseudohermaphroditism
- (3) Both factors possibly increased in 2a above

C CLINICAL

1 Panhypopituitarism

a. Prepuberal

- (1) Frohlich's syndrome
- (2) Loran-Levi infantilism
- (3) Other syndromes

C PHYSICAL STATUS—Especially check

- 1 Weight
- 2 Height
- 3 Bodily contours
- 4 Enlargement of acral parts
- 5 Skin for
 - a Texture
 - b Moisture
 - Acne
 - d Purplish striae
 - e Ecchymoses
- Hair growth
- 7 Facial features
- 8 Visual fields, acuity
- 9 Thyroid gland enlargement
- 10 Blood pressure
- 11 Pulse rate
- 12 Genitalia—external and internal
- 13 Tremor

D LABORATORY DATA

(Note The relative significance of the various tests can be judged under the description of each syndrome)

- 1 Urine (routine)
- 2 Hematology
 - a Red blood cells
 - b Hemoglobin
 - Hematocrit
 - d White blood cells
 - Differential count
- 3 Blood chemical analyses (fasting)
 - a Sugar
 - b Phosphorus (inorganic)
- 4 Function tests
 - Tolerance
 - (1) Glucose—see 103 I J 1
 - (2) Insulin—see 103 I J 2
 - (3) Glucose insulin—see 103 I J 3
 - (4) Creatine—see 103 V A 9
 - b Adrenal water—see 39 XIII A 5 a
 - c Total eosinophilic count—see 39 XIII A 5 b
 - d Epinephrine injection—see 39 XIII A 5 b
 - Adrenocorticotropin injection—see 39 XIII A 5 c
- 5 Miscellaneous test—basal metabolic rate—see 14 XIII D 3
 - Urinary hormone assays
 - a FSH—see 106 I B 1
 - b Estrogens—see 107 V A C
 - 17 ketosteroids—see 107 III A D
 - d 11 oxysteroids—see 107 IV A D

7 Vaginal smears for estrin effect—see 57 XIII E 2**E METHODS FOR SPECIAL PROCEDURES****1 Diabetes insipidus****a Salt loading****(1) Intravenous³**

- (a) Indication—to differentiate between diabetes insipidus and psychogenic polydipsia and polyuria

(b) Method

- [1] Antidiuretic therapy ■ stopped prior to procedure to allow for a return of symptoms
- [2] Fluids restricted for 8 hrs preceding test
- [3] Water taken by mouth 20 cc/kg within 1 hr
- [4] Indwelling catheter is inserted $\frac{1}{2}$ hr after hydration ■ started
- [5] Urine specimens are collected every 15 min
- [6] Output ■ calculated in cc/min
- [7] An infusion of 2.5 per cent sodium chloride is given intravenously after 2 control periods with an adequate urinary excretion (over 5 cc/min)
- [8] Solution is given at a rate of 0.25 cc/kg/min for 45 min
- [9] Pitressin, 0.1 unit, ■ given intravenously if no decrease in urine flow is noted during first 2 postinfusion periods or during infusion

(c) Results in urine flow during and after infusion

- [1] Normal—decreased
- [2] Abnormal—continued diuresis prompt decrease following pitressin

(2) Oral^{7 8}

- (a) Indication—aid in diagnosis of diabetes insipidus
- (b) Method
 - [1] Breakfast omitted

- 69

(2) Method

- (a) No food during the test
- (b) Fluids are restricted after 7 P M the night before procedure
- (c) At 6 A M, patient voids and urine is discarded
- (d) 500 cc of water taken
- (e) All urine is saved from 6 to 9 A M (first specimen)
- (f) At 9 A M, 200 cc of 5 per cent saline (10 Gm salt) injected intravenously
- (g) Second specimen of urine saved from 9 A M to 12 NOON
- (h) Two days later, same procedure is repeated
- (i) Previous evening at 10 P M, 10 mg of desoxycortico sterone acetate given intramuscularly
- (j) Volume of each urine specimen determined and carefully noted
- (k) Sodium and chloride are analyzed in each urine specimen
- (l) Total urinary sodium and chloride ions excreted in first specimen are subtracted from the second (period after the intravenous injection)
- (m) This figure represents the excess over the basal excretion of these ions
- (n) Value in milliequivalents divided by 171 (i.e. milliequivalents in 10 Gm of sodium chloride) yields the fraction of the injected ions excreted
- (o) Comparison of results obtained during the control period and that after the injection of desoxycortico sterone acetate (DOCA) gives the percentage of increased excretion or retention caused by the use of the hormone

(3) Results

- (a) Normal—decrease in urinary excretion of sodium and chloride ions
- (b) Cushing's syndrome—increased

3 Protein metabolism

■ Amino acid (blood) response¹

- (1) Indication—utilization of amino acid may be determined, but to a certain degree only

(2) Method

- (a) Gelatine, 50 Gm in 500 cc of water is given to a fasting subject
- (b) Mixture taken again in 3 hrs
- (c) Blood samples fasting, 1, 2 and 3 hrs
- (d) Amino acids are calculated in mg %

(3) Interpretation

(a) Normal

- [1] First administration—marked rise
- [2] Second administration—slight or no increase

- (b) Pituitary insufficiency—results of second concentration are high or even above the first

- (c) Pituitary dwarfism—normal response

- (4) Comment—test has been used to show that protein metabolism factor is not identical with growth hormone

b Specific dynamic action of protein (S D A) (see 103 IV H)^{1 4}

(1) Indications

- (a) Study of response to ingested proteins by determining effect on basal metabolic rate

- (b) Experimental purposes

(2) Method

- (a) Initial basal metabolic rate is taken after 14 hrs of fasting
- (b) Patient ingests 3 boiled eggs or 200 Gm of boiled chopped beef with a slice of toast and 100 cc of water

[2] Patient given 0.25 Gm of sodium chloride/kg of body weight as a 10 per cent aqueous solution

[3] The following are determined before beginning the test and at hourly intervals for 5 hrs

[a] Blood serum chloride as sodium chloride (mg %)

[b] Urine chloride as sodium chloride (mg/min)

[c] Total urine excreted (cc/min)

(c) Results

[1] Normal

[a] Sodium chloride concentration rises in serum and urine

[b] Urinary minute output—unchanged

[2] Diabetes insipidus

[a] Sodium chloride concentration serum—rises urine—concentration remains very low

[b] Urinary minute output—moderate rise

b Low salt ingestion^{7, 8}

(1) Indication—test for effect on polyuria in diabetes insipidus

(2) Method—approximately 1.5 Gm of sodium chloride allowed per day

(3) Results

(a) Normal—no changes

(b) Diabetes insipidus—urinary volume and chloride concentration decreased

c Water deprivation^{5, 8}

(1) Indication—to determine effect on polyuria in diabetes insipidus

(2) Method

(a) Fluid intake restricted as long as possible usually 24 hrs

(b) Diabetes insipidus patients may not be able to stand thirst variable symptoms may develop

(3) Results

(a) Normal

[1] Total output less than intake

[2] Specific gravity is high

(b) Diabetes insipidus

[1] Total output exceeds intake

[2] Specific gravity rarely over 1.010¹⁰

2 Cushing's syndrome

a Sodium chloride excretion

(1) Indication—aid in diagnosis of adrenocortical hyperfunction

(2) Method

(a) Basic diet (3 days) containing

[1] Chloride 0.95 Gm

[2] Sodium, 0.59 Gm

[3] Potassium, 4.06 Gm

(b) First day

[1] Fluid intake is limited to 20 cc/kg of body weight

[2] Sodium chloride, 10 Gm in capsules in morning and with supper

(c) Second day—repeat as for first day

(d) Third day

[1] Bladder emptied at 8 A.M.

[2] Urine collected from 8 A.M. to 12 noon (4 hrs)

[3] Before 11 A.M., 5 cc of fluid/kg of body weight is given

(e) Amount of chloride in urine specimen is determined

(3) Results

(a) Normal—over 400 mg % of urinary chloride

(b) Decreased amounts

[1] Adrenocortical hyperfunction

[2] Renal concentration impairment

[3] Pregnancy possibly

b Paradoxical excretion of sodium chloride with desoxycorticosterone¹¹

(1) Indication—may be valuable in diagnosis of hyperfunction of adrenal cortex

- (3) Avascular portion of cortex is exposed
 - (4) Arachnoid is punctured with pointed knife
 - (5) Ventricular needle is inserted into each ventricle
 - (6) Fluid is allowed to escape
 - (7) It is replaced by volume of air less than amount removed
 - (8) Soft rubber No. 8 catheter is inserted into ventricle through track of ventricular needle which contained most fluid
 - (9) Scalp is sutured, and catheter is tied in place with black silk thread which was used to close incision
 - (10) Catheter is occluded near scalp with silver clip
 - (11) Cut end of catheter is attached to black silk thread used to close scalp incision on opposite side
 - (12) Wound is covered with small gauze dressing
 - (13) Roentgen studies are then made taking anterior, posterior and lateral stereoscopic views
 - (14) More air can be inserted if ventricular system is incompletely filled
 - (15) Patient is returned to operating room when roentgen plates have been interpreted
 - (16) Catheter is opened, permitting air and fluid to escape and is allowed to drain preventing subsequent cortical bulging and better circulation
 - (17) Craniotomy if indicated
- b Anterior and posterior clinoids may be fused on one or both sides, thus bridging the sella, which is of no clinical significance
 - The anterior clinoids when viewed laterally in roentgen films form a partial roof over the anterior portion of the sella, the posterior clinoids may do the same
- 3 The optic chiasm
 - a Lies upward and anteriorly to
 - (1) Tuberculum sellae
 - (2) Anterior clinoids
 - b May be compressed by a pituitary or another tumor in this region
 - 4 Internal carotid arteries
 - a Location—pass lateral to the dorsum sellae, then wind upward and medial to the anterior clinoids
 - b In this area the arteries are somewhat inferior and posterior to the optic nerves
 - c Aneurysms of these arteries may distort and erode the clinoid processes and the floor of the optic nerve
 - 5 The sphenoid sinus lies anterior and inferior to the sella turcica; pituitary tumor may depress floor of sella into sinus
 - 6 The sixth cranial nerve lies lateral to the internal carotid artery and may be impinged upon by pressure from an aneurysm rarely if ever with pituitary adenoma

B AVERAGE MEASUREMENTS IN ROENTGENOGRAMS (see Chart 11)

- 1 Depth and anteroposterior diameter of lateral contour^{7 1 10 0 4 3} mm

a Birth	25 x 3
b One year	4 x 5
c After 1 year gradual increase to	9 x 11
d Over 18 years	Variations are marked
- 2 Area of lateral contour in square millimeters (Haas method)^{4 15 17 18} sq mm

a Birth	12
b At 3 years rather rapid increase to	48
c Between 20 and 25 years levels off to	74

XIV THE SELLA TURCICA

A CLINICAL IMPORTANCE OF CERTAIN ANATOMIC FEATURES (see Fig. 24)

- 1 Roentgenologic observation of the sella turcica should be made in all cases of suspected or definite pituitary disease
- 2 Clinoid processes (see Fig. 25)
 - a Their position varies, but both (anterior and posterior) pairs usually point in a similar direction and any change in this respect may indicate pressure (see below)

- (c) Basal metabolic rate is repeated in 2 hrs, during which time the patient remains resting in a reclining position

(3) Results

- (a) Normal—rate is increased by 14 to 18 per cent
- (b) Endocrine diseases—normal in majority (see specific chapters)
- (c) Simple obesity—may be decreased
- (d) Undernutrition—may be increased

F ROENTGENOGRAPHIC FINDINGS

1 Skull for

- a Sella enlargement (see below)
- b Other abnormalities

2 Hand wrist for bone age

3 Bone texture in

- a Lumbosacral spine
- b Pelvis

4 Flat plate of abdomen and/or air in sufflation

5 Arteriography (see Figs 25, 26)

- a Indications—should be judged by competent neurosurgeon

- b Purpose—arteriography (first introduced by Moniz⁹) is

- (1) Means for visualizing intracranial aneurysms
- (2) Useful in differential diagnosis of tumors in or about the sella turcica (see 2 XIV H)

■ Data suggesting aneurysm¹⁴

PER CENT

(1) Subarachoid hemorrhage	75
(2) Cranial nerve involvement	46
(3) Headache	
(a) Generalized	40
(b) Unilateral	43
(4) Facial pain	7
(5) Convulsions	10
(6) Vertigo	10
(7) Hypopituitarism and myxedema	3
(8) Roentgen evidence suggesting aneurysm—thinning of lateral margin of optic foramen (see 2 XIV H 1, Fig 26) ⁸	

d Technique¹⁴

- (1) All patients should be tested for sensitivity to iodine because diodrast is used

- (2) Selection of side to inject is often possible from

- (a) History
- (b) Physical signs

- (3) Closed method of injection

- (4) Pentothal anesthesia (following encephalogram)

- (5) Patient

- (a) Is kept on carrier stretcher which is made immobile

- (b) Lies on back, with pillow under shoulder blades and with two Turkish towels under occiput

- (6) Needle (2 in, 18 gauge) is

- (a) Attached to 20 cc Luer Lok syringe with 2 way stop cock containing citrate solution

- (b) Directed to penetrate adventitia from 1 to 2 cm below bifurcation of common carotid artery

- (7) Several injections of citrate solution are made to ensure free flow, with needle well in and directed toward lateral wall of artery

- (8) Syringe with 20 cc of diodrast is connected

- (9) Preparations made for roentgen exposures, using upright automatic Bucky for stereoscopic views

- (10) Fifteen cc of diodrast injected rapidly

- (11) First roentgen exposure made

- (12) Remainder of solution (5 cc) given during automatic shifting of roentgen tube

- (13) Second exposure taken

■ Ventriculography^{5 23}

- a Indication—localization of tumor extension of pituitary adenomas

b Method

- (1) Burr opening 3.5 cm on both sides midline in parieto occipital region after proper preparation
- (2) Dura is opened

- 2 *Technic of measuring lateral contour areas by method of Haas*²⁰
 - a Stereoscopic films are necessary
 - b Tuberculum sella and tips of posterior clinoids are identified, and the midpoint between the latter on the upper dorsum is marked
 - A line is drawn between the tuberculum sella and midpoint of the posterior clinoids
 - d The lateral contour is
 - (1) Outlined on the film with a fine pointed grease pencil
 - (2) Traced upon semitransparent sq mm ruled paper
 - (3) Sketched directly on the paper if the inner border of the sella is distinct
 - Squares are counted
 - f If the right and the left contours differ in size, the two areas are outlined
 - g Unilateral enlargement is not uncommon from aneurysm and tumor
 - 3 Measurements of width of dorsum, in terclinoid spaces and floor of sella are helpful in special cases, as unilateral tumors with or without erosion¹⁸
- G INTERPRETATION OF VARIATIONS IN SIZE OF LATERAL CONTOUR AREAS**
- 1 Since enlargement of the sella does not necessarily mean the presence of a tumor, no definite measurements may be cited which would ensure the diagnosis of pituitary tumor
 - 2 Pituitary tumors of clinical significance may be present without enlargement of the sella but this is rare
 - 3 Of 1 000 pituitary glands examined at postmortem, adenomas were found from 1 mm up to a size which occupied the entire sella yet none was considered clinically significant⁸
 - 4 Areas
 - a To 150 sq mm—not uncommonly found without evidence of pituitary dysfunction or pressure
 - b Above 150 sq mm—usually indicate pituitary tumor, frequently with clinical signs and/or symptoms
 - 5 Enlargement of the sella may occur without pituitary tumor in
 - a Cretinism
 - b Suprasellar cyst
 - Women past 40 years of age who have been castrated before 25 years of age⁴⁴
 - d Hydrocephalus
 - e Chronic increased intracranial pressure from any cause
 - f Hypertension⁴⁵
 - 6 Procedures for problem of enlarged sella found unexpectedly on roentgenography of skull
 - a Careful inspection for other abnormalities of skull (see below)
 - b Clinical appraisal for hormonal changes of hyper or hypopituitarism
 - c Visual field examination for evidence of optic nerve pressure
 - d Headache
 - (1) If persistent and impressive roentgen therapy may be tried
 - (2) Avoid informing the neurotic patient of 'tumor in the head' and defer roentgen therapy
 - (3) Re examine at later date for further enlargement and other unusual findings
- H OTHER ROENTGENOGRAPHIC OBSERVATIONS ON THE SELLA**¹⁶ (see Fig 26)
- 1 Abnormal position or calcium content of anterior clinoids
 - a Unilateral elevation of 1 anterior clinoid with erosion—typical of an aneurysm
 - b Bilateral elevation—intrasellar lesion
 - 2 Abnormal position, decreased calcium content or destruction of posterior clinoids—intrasellar or suprasellar lesion
 - 3 Depression and thinning of floor into sphenoid sinus—frequent in pituitary adenomas
 - 4 Suprasellar calcification—suggestive of suprasellar tumor
 - 5 Intrasellar calcification—may represent old infarction or inactive tumor
 - 6 Calcification of internal carotid arteries, as shown by calcium deposits lateral to anterior clinoids—indicate arteriosclerosis
 - 7 Abnormalities of skull which may indicate hyperpituitarism
 - a Sinus enlargement
 - b Prognathism
 - Texture of tables

- 3 Dorsum—^{11 12 13 14 15 16 17 18 19 20 21} mm
- a Birth 6.75
- b At 10 years, increases to 7.5
- Adulthood 12 to 18
- C RELATIONSHIP OF SELLA TO SIZE OF SKULL
- 1 ■ 21 22 23 24 25 26 27 28 29 30 31 32 33 ■
- 1 Skull at birth ■ approximately two thirds of its adult size
- 2 Increase ■ size of sella with growth is relatively much greater than that of the skull
- 3 Size of skull ■ not a suitable standard for comparison of sella size
- D VOLUME AND WEIGHT
- 1 Average volume of sella turcica as compared with volume displaced by hypophysis²¹
- a Sella (denuded of all tissues, based on measurements of 70 cadavers)—1.20 cc
- b Hypophysis—0.57 cc
- c Range for either—0.75 to 2.0 cc
- 2 Estimated volume from roentgenologic measurements
- a Attempts to estimate volume of sella by measurements of lateral contour area and width of dorsum (Kovacs²²) are said to correlate with injection methods in the cadaver but confirmatory evidence is needed
- b Efforts to determine a more constant estimate of sella size in relation to age sex and height by measurements of floor, dorsum, interclinoid spaces lateral contour areas as well as depth anterior and posterior diameters have been disappointing^{17 24}
- Even if the sella volume could be measured accurately from roentgenograms the size of the hypophysis would remain unknown because
- (1) An enlarged sella does not always contain a corresponding increase in size of the pituitary gland²
- (2) Considerable hypertrophy of the gland may take place before the sella increases in size²⁵
- (3) Tumors may grow out through diaphragm without affecting the size of the sella¹⁷
- 3 Average weight of hypophysis^{1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100} Gm
- a Birth (variations 0.05 to 0.1) 0.1
- b 7 years 0.5
- c 25 to 45 years (variations 0.3 to 0.5) 0.6
- d 45 years and over 0.5
- E HEIGHT AGE AS A STANDARD FOR SIZE OF LATERAL CONTOUR AREA²⁶
- 1 The sella increases with age in normal children
- 2 Height age (■, normal average height for ■ given chronologic age as shown by height charts) is a good index of somatic and skeletal development in the normal as well as in the abnormal, with the exception of chondrodystrophy
- 3 Chondrodystrophy—sella is
- a Normal average size for any given chronologic age
- b Relatively large for height age thus the latter cannot be used ■ an index
- 4 Dwarfs without pituitary, suprasellar tumors or intracranial pressure—the sella is often smaller than would be expected for height age (see Protocol 3 IV)²⁷
- 5 Cretins
- a The sella is large for height age as well as for chronologic age in some cases (see 24 VIII A 1)²⁸
- b This confirms the findings of enlarged pituitaries at postmortem¹⁹
- 6 Hypertension—Ziskin reports larger sellas than normal¹⁵
- 7 Trends are most likely to be manifested in a series rather than in individual cases
- F MEASUREMENT OF LATERAL CONTOUR AREA
- 1 Introduction
- a A more accurate measurement of contour area than the use of 2 diameters (AP and depth)
- b Changes in size from time to time may be more easily detected
- c Areas may be estimated in most cases by the use of the sellameter, which eliminates outlining the contour on transparent paper (see Chart 12)

- pituitary *J Biol Chem* 147 77 (Jan) 1943
- 36 McConnell A A Case of diabetes insipidus influenced by partial thyroidectomy *Int J M Sc pp* 742 745 (Dec) 1936
 - 37 Minkowski O Über einen Fall von Akromegalie *Berlin klin Wchnschr* 24 371 374 1887
 - 38 Mohr B Hypertrophie der Hypophysis cerebri und dadurch bedingter Druck auf die Hirn grundfläche insbesondere auf die Schnerven das Chiasma derselben und den hintere Hirnschenkel *Wechschr f d ges Heilk Berln* 565 571 1840
 - 39 Oliver G and Schafer E A On physiological action of extracts of pituitary body and certain other glandular organs *J Physiol* 18 276 279 1895
 - 40 Paulesco Nicholas L'hypophyse du cerveau I *Physiologie Paris* 1908
 - 41 Paultauf A Der Zwergwuchs in gerichtlicher und anatomischer Beziehung Wien 1891
 - 42 Philipp E Hypophysenvorderlappen und placenta *Zentralbl f Gynak* 54 450 453 (Feb) 1930
 - 43 Rasmussen A T A quantitative study of the human hypophysis cerebri or pituitary body *Endocrinology* 8 509 524 (July) 1924
 - 44 Rathke Martin Heinrich Über die Entstehung der Glandula pituitaria *Arch f Anat Physiol u wiss Med* 482 485 1838
 - 45 Riddle O Bates R W and Dykshorn S W A new hormone of the anterior pituitary *Proc Soc Exper Biol & Med* 29 1211 1212 (July) 1932
 - 46 Rogowitsch N Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse *Beitr z path Anat u z allg Path* 4 453 470 1888 1889
 - 47 Santorini G D *Observationes anatomicae* p 70 Venet 1724
 - 48 Saurerotte N Accroissement singulier en gros seur des os d'un homme age de 39 ans *Mémoires de Chirurgie Paris* 1 407 411 1801
 - 49 Schapiro H Kann man mit Hypophysenvorderlappen den unterentwickelten männlichen Genitalapparat beim Menschen zum Wachstum anregen *Deutsche med Wchnschr* 56 1605 1607 (Sept) 1930
 - 50 Schloffer H Zur Frage der Operationen an der Hypophyse *Beitr z klin Chir* 1 767 817 1906
 - 51 Sheehan H L and Murdock R Postpartum necrosis of anterior pituitary effect of subsequent pregnancy *Lancet* 1 132 135 (July) 1938
 - 52 Simmonds M Über Hypophysenschwund mit todtlichem Ausgang *Deutsche med Wchnschr* 40 322 323 1914
 - 53 Smith F and Smith I P Repair and activation of thyroid in hypophysectomized tadpole by parenteral administration of fresh anterior lobe of bovine hypophysis *J M Research* 43 267 283 (June July) 1922
 - 54 Soemmerring S T von *Dissertatio de Basi Encephali et Originibus Nervorum* Gottinga 1778
 - 55 Starling E H and Varney E B The secretion of urine as studied on the isolated kidney *Proc Roy Soc* 97 321 363 1924
 - 56 Stricker P and Grueter F Action du lobe antérieur de l'hypophyse sur la montée lactée *Compt rend Soc de biol* 99 1978 1980 (Jan) 1928
 - 57 Tamburini A Beitrag zur Pathogenese der Akromegalie *Centralbl f Nerven u Psychiat* 5 625 630 1894
 - 58 Teel H M and Watkins O Effect of extracts containing growth principle of anterior hypophysis upon blood chemistry of dogs *Am J Physiol* 89 662 685 (Aug) 1929
 - 59 Uhlenhuth E and Schwartzbach E Hypophysis and thyroid gland *Proc Soc Exper Biol & Med* 26 149 154 (Nov) 1928
 - 60 Vassale G and Sacchi E Sulla distruzione della ghiandola pituitaria *Riv sper di freniat* 18 525 561 1892
 - 61 Verga A Caso singolare di prospectasia *rendiconti del Reale Istituto di Lombardo Milano* 1 111 117 1864 *Nouv icon de la Sape* Vol I 1889
 - 62 Vesulius Andreas De humani corporis fabrica *Basilea Oporinus* 1543
 - 63 Wadsworth O F A case of myxoedema with atrophy of the optic nerves *Boston M & S J* 112 58 (Jan) 1885
 - 64 Willis T *Anatomie cerebri Omnia Opera Venetiae* 1/08 Chap 14 p 134
 - 65 Young F G Permanent experimental diabetes produced by pituitary (anterior lobe) injections *Lancet* 2 372 374 (Aug) 1937
 - 66 Zondek H and Aschheim S Das Hormon des Hypophysenvorderlappens testobjekt zum Nachweis des Hormons *Klin Wchnschr* 6 243 252 (Feb) 1927
 - 67 — Das Hormons des Hypophysenvorderlappens Darstellung chemische Eigenschaften biologische Wirkungen *Klin Wchnschr* 7 831 835 (Apr) 1928
- ## II ANATOMY
- 1 Abt I A *Abts Pediatrics* Vol 1 378 Philadelphia Saunders 1923
 - 2 Cowdry E V *A Textbook of Histology* Philadelphia Lea & Febiger 1934 p 190
 - 3 Gray H *Anatomy of Human Body* ed 23 Philadelphia Lea & Febiger 1936 p 1264
 - 4 Harns G W Induction of ovulation in rabbit by electrical stimulation of hypothalamophyseal mechanism *Proc Roy Soc London* s B 122 374 394 (May) 1937
 - 5 Heubcker P and White H L Hypothalamophyseal system and its relation to water balance in the dog *Am J Physiol* 133 582 593 (Apr) 1941
 - 6 Rasmussen A T *Pituitary Gland* p 118 Baltimore Williams & Wilkins 1938
 - 7 — The weight of the principal components of the normal male adult human hypophysis cerebri *Am J Anat* 42 1 27 (Aug) 1928
 - 8 — The weight of the principal components of the normal hypophysis cerebri of the adult human female *Am J Anat* 55 253 275 (Sept) 1934
 - 9 — Innervation of the hypophysis *Endocrinology* 23 263 278 (Sept) 1938
 - 10 Wislocki G H *Pituitary Gland* pp 48 67 Baltimore Williams & Wilkins 1938
- ## III EMBRYOLOGY
- 1 Arey L *Developmental Anatomy* ed 3 p 412 Philadelphia Saunders 1936
- ## IV CONGENITAL ANOMALIES
- 1 Bryant W S The clinical possibilities of the pharyngeal pituitary *M Rec* 90 441-444 (Sept) 1916

- 8 Encephalograms reveal extension of pituitary tumor
 - a Upward distention of capsule into suprasellar space
 - b Laterally

- 9 Arteriograms show arterial aneurysms causing unilateral enlargement of sella turcica simulating an intrasellar tumor (see 2 VIII F 5)

REFERENCES

I HISTORY

- 1 Allen H M Effects of the extirpation of the anterior lobe of the hypophysis of *Rana pipiens* Biol Bull 37 117 130 1917
- 2 Aicheim S and Zondek B Schwangerchaftsdiagnose aus dem Harn (durch Hormonnachweis) Klin Wchnschr 78 9 (Jan) 1928
- 3 Aicheim H Demonstration von hunden nach Extirpation Hypophyse (kurze Mitteilung) Wien klin Wchnschr 22 1730 1909
- 4 Babin L J Tumeur du corps pituitaire sans acromégalie et avec arrêt de développement des organes génitaux Rev neurol 8 531 533 1900
- 5 Barnes B O Regan J F, and Burno J G Is there specific diuretic hormone in anterior pituitary? Am J Physiol 105 559 561 (Sept) 1933
- 6 Bartels M Ueber die Beziehungen von Veränderungen der Hypophyse enggehend zu Misswachsstum und Genitalstörungen (Dystrophia adiposo genitalis) München med Wchnschr 4 201 (Jan) 1903
- 7 Bell W B Pituitary body and the therapeutic value of the infundibular extract in shock uterine atony and intestinal paresis Brit M J 2 1609 1613 1909
- 8 Benda C Ueber den normalen Bau und einige pathologische Veränderungen der menschlichen Hypophysis cerebri Arch f Anat u Physiol Physiol Abthlg 3758 3 373 380 (Feb) 1900
- 9 Caton H and Paul F T Notes on a case of acromegaly treated by operation Brit M J 2 1421 1423 1893
- 10 Cole H H, and Hart G H Sex hormones in blood serum of mares sera of mares from 22nd day of pregnancy to first heat period postpartum Am J Physiol 94 597 603 (Sept) 1930
- 11 Collip J B, Anderson E M and Thomson D L Adrenocorticotrophic hormone of anterior pituitary lobe Lancet 2 347 348 (Aug) 1935
- 12 Collip J B and Anderson E M The production of serum inhibitory to the thyrotrophic hormone Lancet 1 76 78 1934
- 13 Comte L Contribution à l'étude de l'hypophyse humaine Thèse de doctorat Lausanne 1895
- 14 Crowe S J Cushing H W and Homans J Experimental hypophysectomy Bull Johns Hopkins Hosp 21 127 169 1910
- 15 Cushing H W Sexual infantilism with optic atrophy in cases of tumor affecting the hypophysis cerebri J Nerv & Ment Dis 33 704 716 1906
- 16 Cushing H Dyspituitarism twenty years later with special consideration of pituitary adenoma Arch Int Med 51 487 557 (Apr) 1933
- 17 Dale H H The action of extracts of the pituitary body Biochem J 4 427-447 1907
- 18 Engle E T Effect of daily tran plants of anterior lobe from gonadectomized rats on immature test animals Am J Physiol 88 101 106 (Feb) 1919
- 19 Evans H M, and Long J A The effect of the anterior lobe administered intraperitoneally upon growth maturity and oestrus cycles of the rat Anat Rec 21 62 63 (Mar) 1921
- 20 Erdheim J Namosoma pituitaria Beitr z path Anat u z allg Path 67 307 377 1916
- 21 Faneau de la Cour F V Du féminisme et de l'infantilisme chez les tuberculeux Paris Thèse No 1 1871
- 22 Fisher C, Ingram W R, and Ranson S W Relation of hypothalamic hypophyseal system to diabetes insipidus Arch Neurol & Psychiat 34 124 163 (July) 1935
- 23 Frank J P De curandis hominum morbis epitome Liber v Mannheim 1794
- 24 Fritzsche and Klebs H Ein Beitrag zur Pathologie des Reizenwachses klinische und pathologische anatom Untersuchungen Leipzig F C W Vogel 1884
- 25 Frohlich A Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie Wien klin Rundschau 15 833 836 and 906 905 1901
- 26 Galen Claudius quoted by Rolleston H D The Endocrine Organs in Health and Disease p 42 London Oxford 1936
- 27 Goldzieher M Ueber Sektionsbefunde bei Diabetes Insipidus Verhandl d deutsch path 16 281 287 1913
- 28 Haen Anton de De Crani uestione Ratio Medendi Vennae 1759 Vol 6 pp 264 272
- 29 Hirsch O Über endonatale Operationsmethoden bei Hypophysis Tumoren Berlin klin Wchnchr 48 1933 1935 1911
- 30 Hoffbauer J Die Aetiologie der Eklampsie Zentralbl f Gynak 42 745 757 1918
- 31 Horley V Functional nervous disorders due to loss of thyroid gland and pituitary body Lancet 1 5 (Jan) 1886
- 32 Houssay B A and Basotti A La diabetes pancreatica de los perros hipofisoprivos Rev Soc argent de biol 6 251 295 1930
- 33 Kamm O Aldrich T P Grote I W Rowe L W, and Bugbee H P The active principles of the posterior lobe of the pituitary gland I The demonstration of the presence of two active principles II The separation of the two principles and their concentration in the form of potent solid preparations J Am Chem Soc 50 573 (Feb) 1928
- 34 Marie Pierre Sur deux cas d'acromégalie hypophtique singulière non congénitale des extrémités supérieures inférieures et céphalique Rev de Méd 5 297 333 1886
- 35 Marx W Simpson M E and Evans H M Purification of growth hormone of anterior

- 15 Fraenkel Conrat J, Fraenkel Conrat H and Evans H M Effects of purified pituitary preparations on nonprotein nitrogen constituents of blood *Am J Physiol* 137 200 212 (Aug) 1942
- 16 Freud J, Levie L H and Kroon D B Observations on growth (chondrotrophic) hormone and localization of its point of attack *J Endocrinol* 1 56 64 (June) 1939
- 17 Gaarenstroom J H, Huble J and de Jongh N E The diabetogenic activity of growth promoting extracts in rats *J Endocrinol* 6 71 74 (Apr) 1949
- 18 Gaebler O H Some effects of anterior pituitary extracts on nitrogen metabolism, water balance and energy metabolism *J Exper Med* 57 349 363 (Mar) 1933
- 19 Gaebler O H and Price W H Effects of an anterior pituitary growth preparation on protein metabolism *J Biol Chem* 121 497 506 (Nov) 1937
- 20 Greaves J D, Frieberg I K and Johns H E Preparation and assay of anterior pituitary fractions rich in ketogenic and respiratory quotient producing substances *J Biol Chem* 133 243 (Dec) 1939
- 21 Harrison H C and Long C N Effects of anterior pituitary extracts in fasted rat *Endocrinology* 26 971 978 (June) 1940
- 22 Herring V V, and Evans H M Effects of purified anterior pituitary hormones on carbohydrate stores of hypophysectomized rats *Am J Physiol* 140 452-459 (Dec.) 1933
- 23 Houssay B A and Anderson E Diabetogenic action of purified anterior pituitary hormones *Endocrinology* 45 627 629 (Dec) 1949
- 24 Lee M O Relation of anterior pituitary growth hormone to protein metabolism *Proc A Research Nerv & Ment Dis* 17 193 221 1938
- 25 Lee M O and Schaffer N K Anterior pituitary growth hormone and the composition of growth *J Nutrition* 7 337 363 (Mar) 1934
- 26 Li C H, Geschwind I and Evans H M The effect of growth hormone on the inorganic phosphorus levels in the plasma *Endocrinology* 44 67 70 (Jan) 1949
- 27 Li C H, Simpson M E and Evans H M The gigantism produced in normal rats by injection of the pituitary growth hormone III Main chemical components of the body *Growth* 12 39 42 (Jan) 1948
- 28 Long C N Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 4th Meeting June 11 12 New York Josiah Macy Jr Foundation 1943 p 122
- 29 Marx W, Magy D B, Simpson M E and Evans H M Effect of purified pituitary preparations on urine nitrogen in rat *Am J Physiol* 137 544 550 (Oct) 1942
- 30 Milman A E and Russell J A Some effects of purified pituitary growth hormone on carbohydrate metabolism in the rat *Endocrinology* 47 114 128 (Aug) 1950
- 31 Milton D L Pituitary Gland p 193 Baltimore Williams & Wilkins 1938
- 32 Mirsky A and Swadesh N The influence of the anterior pituitary gland on protein metabolism *Am J Physiol* 123 148 149 (July) 1938
- 33 Mirsky I A Influence of anterior pituitary gland on protein metabolism *Endocrinology* 25 52 56 (July) 1939
- 34 Paschke E E Influence of anterior pituitary extract on protein and carbohydrate metabolism *Am J Physiol* 136 128-135 (Mar) 1942
- 35 Pugsley L I and Anderson E M The effect of the growth and thyrotropic hormones of the anterior pituitary upon the calcium metabolism of the rat *Am J Physiol* 109 85 (July) 1934
- 36 Reid E Test methods for the diabetogenic activity of pituitary preparations *J Endocrinol* 6 45 (Apr) 1949
- 37 Reinhardt W O Essays in Biology p 489 Berkeley Univ California Press 1943
- 38 Reiss M Influence of the pituitary anterior lobe upon the specific dynamic action of protein *J Endocrinol* 2 329 338 (Aug) 1940
- 39 Schaffer N K and Lee M Effect of anterior pituitary growth hormone on protein metabolism *J Biol Chem* 108 355 371 (Feb) 1935
- 40 Scott J L Jr and Engel F L The role of hormones in adipose glycogen synthesis in the rat Anterior pituitary growth hormone *Endocrinology* 46 582 585 (June) 1950
- 41 Scow R O and Marx W Effect of growth hormone in rats thyroidectomized at birth *Anat Rec* 88 456-457 (Apr) 1944
- 42 Segaloff A and Nelson W Growth and development of 6 generations of thyromized albino rats *Am J Physiol* 130 671 674 (Oct) 1940
- 43 Silberberg M Effects of extract of cattle anterior pituitary gland on endochondral ossification in young guinea pigs *Proc Soc Exper Biol Med* 32 1423 1425 (June) 1935
- 44 Silberberg M and Silberberg R Growth processes in cartilage and bone subsequent to gonadectomy and administration of anterior pituitary extract of cattle in immature male and female guinea pigs *Am J Path* 15 55 72 (Jan) 1939
- 45 Szego C M and White A The influence of growth hormone on fasting metabolism *Endocrinology* 44 150 166 (Feb) 1949
- 46 Teel H M and Cushing H Studies in the physiological properties of the growth promoting extracts of the anterior hypophysis *Endocrinology* 14 157 163 (May June) 1930
- 47 Teel H M and Watkins O The effect of extracts containing the growth principle of the anterior hypophysis upon the blood chemistry of dogs *Am J Physiol* 80 662 685 (Aug) 1929
- 48 Young F Growth and diabetes in normal animals treated with pituitary (anterior lobe) diabetogenic extract *Biochem J* 39 515 536 1945

B Individual Hormones

4 Gonadotropic Hormones

- 1 Astwood E B Regulation of corpus luteum function by hypophyseal luteotrophin *Endocrinology* 28 309 320 (Feb) 1941
- 2 Astwood E B and Fevold H L Action of progesterone on gonadotropic activity of pituitary *Am J Physiol* 127 192 193 (Aug) 1939
- 3 Brewer J I, Jones H O and Skiles J H Jr Effect of gonadotropic substance on ovulation results of intramuscular use of preparation of high potency from pregnant mare serum *JAMA* 118 278 283 (Jan) 1942

- 2 Lyon I P Adipose and lipomatosis Arch Int Med 6 120 1910
- 3 Zondek H Diseases of the Endocrine Glands ed 3 p 260 Baltimore Williams & Wilkins 1944

V HISTOLOGY

- 1 Addison W H The cell changes in the hypophysis of the albino rat after castration J Comp Neurol 28 441-461 1917
- 2 Biggart J H Hypophysis of human castrate Bull Johns Hopkins Hosp 54 157 164 (Mar) 1934
- 3 — Some observations on basophil cells of human hypophysis Tr Edinburgh Obst Soc 42 113 124 1935
- 4 Bowen H H The origin of secretory granules, Proc Nat Acad Sc 9 349 352 (Aug) 1923
- 5 — The cytology of glandular secretion Quart Rev Biol 4 484 519 (Dec) 1929
- 6 Comte L Contribution à l'étude de l'hypophyse humaine Thèse de doctorat Lausanne 1893
- 7 Erdheim J and Stumme E Über die Schwangerschaftsveränderung der Hypophyse Beitr z path Anat u z allg Path 46 1 132 1909
- 8 Fichera G Sur l'hypertrophie de la glande pituitaire consécutive à la castration Arch Ital de biol 43 405-426 1905
- 9 Gotthalk H C, and Tilden I L Necrosis of anterior pituitary following parturition JAMA 4 114 33 35 (Jan) 1940
- 10 Kirkman H A cytological study of the anterior hypophysis of the guinea pig and a statistical analysis of its cell types Am J Anat 61 233 287 1937
- 11 Lehmann J Zur Frage der Geschlechtsspezifität der Keimdrüseninkrete Inkretwirkung und Veränderung der Kastrationshypophyse der Ratte Arch f d ges Physiol 216 729 748 1977
- 12 Rasmussen A T The percentage of the different types of cells in the anterior lobe of the hypophysis in the adult human female Am J Path 9 459-471 (July) 1933
- 13 — Pituitary Gland p 118 Baltimore Williams & Wilkins 1938
- 14 Schleidt J Ueber die Hypophyse bei feminenten Männchen und maskulierten Weibchen Zentralbl f Physiol 27 1170 1172 1914
- 15 Severinghaus A E A cytological study of the anterior pituitary of the rat with special reference to the Golgi apparatus and to cell relationship Anat Rec 57 149 175 (Sept) 1933
- 16 — The cytology of the pituitary gland Proc A Research Nerv & Ment Dis 17 69 117 (Dec) 1936
- 17 — Cellular changes in the anterior hypophysis with special reference to its secretory activities Physiol Rev 17 556 588 1937
- 18 — Pituitary Gland p 69 Baltimore Williams & Wilkins 1938
- 19 — Cytology of anterior pituitary gland of postmenopausal woman J Clin Endocrinol 4 583 585 (Dec) 1944
- 20 Severinghaus A E Smelser B K and Clark H M Anterior pituitary changes in the adult male rat following thyroidectomy Proc Soc Exper Biol & Med 31 1127 1129 (June) 1934
- 21 Spark C Relation between basophilic invasion of the neurohypophysis and hypertensive disorders Arch Path 19 473 501 (Apr) 1935

- 22 Stein S I Experimental studies on the hypophysis cerebri III The effect of several pregnancies in the albino rat Endocrinology 18 721 729 (Nov Dec) 1934
- 23 Wolfe J M and Cleveland H Pregnancy changes in the anterior hypophysis of the albino rat Anat Rec 56 33 45 (Apr) 1933

VI FUNCTIONS

B Individual Hormones

3 Growth Hormone

- 1 Ayres G B and Lee M Determination of nitrogen partition in tissues J Biol Chem 115 139 148 (Aug) 1936
- 2 Becks H Collins D A, Asling C W, Simpson M F, Li C H, and Evans H M The gigantism produced in normal rats by injection of the pituitary growth hormone V Skeletal changes skull and dentition Growth 11 55 67 (Jan) 1948
- 3 Becks H Simpson M E Marx W Li C H and Evans H M Antagonism of pituitary adrenocorticotrophic hormone (ACTH) to action of growth hormone on osseous system of hypophysectomized rats Endocrinology 34 311 316 (May) 1944
- 4 Campbell J Davidson I W F and Lei H P The production of permanent diabetes by highly purified growth hormone Endocrinology 46 585 590 (June) 1950
- 5 Campbell J Davidson I W F Snare W D and Lei H P Diabetogenic effect of purified growth hormone Endocrinology 46 273 281 (Mar) 1950
- 6 Cotes P M Reid E and Young F G Diabetogenic action of pure anterior pituitary growth hormone Nature 164 209 211 (Aug) 1949
- 7 Evans H M Becks H A Long C W Simpson M E and Li C H The gigantism produced in normal rats by injection of the pituitary growth hormone IV Skeletal changes tibia costochondral junction and caudal vertebrae Growth 12 48 54 (Jan) 1948
- 8 Evans H M Meyer K Simpson M E and Reichert F L Disturbance of carbohydrate metabolism in normal dogs injected with the hypophyseal growth hormone Proc Soc Exper Biol & Med 29 857 858 (Apr) 1933
- 9 Evans H M Meyer K and Simpson M Growth and Gonad Stimulating Hormones of Anterior Hypophysis Vol 2 pp 229 252 409 442 Berkeley Univ California Press 1933
- 10 Evans H M and Simpson M E Hormones of the anterior hypophysis Am J Physiol 98 511 546 (Oct) 1931
- 11 Evans H M Simpson M E and Li C H The gigantism produced in normal rats by injection of the pituitary growth hormone I Body growth and organ changes Growth 12 15 32 (Jan) 1948
- 12 Evans H M Asling C W Simpson M E and Becks H The growth of hypophysectomized female rats following chronic treatment with pure pituitary growth hormone Growth 13 191 206 1949
- 13 Fraenkel Conrat H Chemistry of the hormones Ann Rev Biochem 12 273 304 1943
- 14 Fraenkel Conrat H Simpson M E and Evans H M Effect of hypophysectomy and of purified pituitary hormones on liver arginase activity of rats Am J Physiol 138 439 449 (Feb) 1943

glands of male ground squirrel *Endocrinology*
28 521 530 (Apr) 1941

II Individual Hormones

5 Thyrotropic Hormone (TSH)

- 1 Aird R II Experimental exophthalmos and associated myopathy induced by thyrotropic hormone *Ann Int Med* 15 564 581 (Sept) 1941
- 2 Albert A Experimental production of exophthalmos in *Fundulus* by means of anterior pituitary extracts *Endocrinology* 37 389 406 (Dec) 1945
- 3 Anderson E M and Collip J II Thyrotropic hormone of anterior pituitary *Proc Soc Exper Biol & Med* 30 680 683 (Feb) 1933
- 4 Aron M Action de la préhypophyse sur la thyroïde chez la cobaye *Compt rend Soc de biol* 102 682 684 (Nov) 1929
- 5 — Particularités histologiques de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse *Compt rend Soc de biol* 103 143 147 (Jan) 1930
- 6 Baumann E J and Marine D Glycosuria in rabbits following injections of saline extract of anterior pituitary *Proc Soc Exper Biol & Med* 29 1220 1223 (June) 1932
- 7 Benedict E B Putnam T J and Teel H M Early changes produced in dogs by the injection of a sterile active extract from the anterior lobe of the hypophysis *Am J M Sc* 179 489 497 (Apr) 1930
- 8 Buhler F Tierexperimentelle Untersuchungen über den Einfluss von verschiedenen Hormonen auf die Ausscheidung von Kreatin und Kreatinin im Urin *Ztschr f d ges exper Med* 96 821 844 1935
- 9 Closs K Loeb L and Mackay E The effect of an acid extract of the anterior pituitary on the iodine concentration of the blood and thyroid gland *J Biol Chem* 96 585 591 (June) 1932
- 10 Dobyns B M Studies on exophthalmos produced by thyrotropic hormone study of exophthalmos produced by various thyrotropic hormones and influence of testes on exophthalmos *Surg Gynec & Obst* 82 290 300 (Mar) 1946
- 11 — Studies on exophthalmos produced by thyrotropic hormone changes induced in various tissues and organs (including orbit) by thyrotropic hormone and their relationship to exophthalmos *Surg Gynec & Obst* 82 609 617 (May) 1946
- 12 Eitel H and Lexer E W Schilddrüsenatrophie und Frakturheilung *Arch f klin Chir* 185 587 598 1936
- 13 Foster G L and Smith P E Hypophysectomy and replacement therapy in relation to basal metabolism and specific dynamic action in rat *JAMA* 87 2151 2153 (Dec) 1926
- 14 Fraenkel Conrat J Fraenkel Conrat II and Evans H M Effects of purified pituitary preparations on nonprotein nitrogen constituents of blood *Am J Physiol* 137 200 212 (Aug) 1942
- 15 Fraenkel Conrat H L Simpson M E and Evans H M Effect of purified pituitary preparations on liver weights of hypophysectomized rats *Am J Physiol* 135 398-403 (Oct) 1941
- 16 Friedgood H II Experimental exophthalmos and hyperthyroidism in guinea pigs *Bull Johns Hopkins Hosp* 54 48 73 (Jan) 1934
- 17 Hogben L T Studies on internal secretion. I The effect of pituitary (anterior lobe) injection upon normal and thyroidectomized axolotls *Proc Roy Soc, London s B* 24 204 215 (Jan) 1923
- 18 Houssay A Bissotti A and Magdalena A Hipofisis y tiroidea acción del extracto del lóbulo anterior de la hipófisis sobre la histología de la tiroidea del perro *Rev Soc argent de biol* 130 143 (May June) 1932
- 19 Loeb L and Bassett R II Effect of hormones of anterior pituitary on thyroid gland in the guinea pig *Proc Soc Exper Biol & Med* 26 860 862 (June) 1929
- 20 — Comparison of effects of various preparations of anterior pituitary gland on thyroid of guinea pig *Proc Soc Exper Biol & Med* 27 490-492 (Mar) 1930
- 21 Loeb L Bassett R B and Friedman H Further investigation concerning the stimulating effect of anterior pituitary gland preparation on the thyroid gland *Proc Soc Exper Biol & Med* 28 209 213 (Dec) 1930
- 22 Loeb L and Friedman H Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle *Proc Soc Exper Biol & Med* 29 648 650 (Feb) 1932
- 23 Marine D Studies on pathological physiology of exophthalmos of Graves disease *Ann Int Med* 12 443 453 (Oct) 1938
- 24 Marine II and Rosen S H Effect of thyrotropic hormone on auto and homeotransplants of the thyroid and its bearing on question of secretory nerves *Am J Physiol* 107 677 680 (Mar) 1934
- 25 — Exophthalmos in thyroidectomized guinea pigs by thyrotropic substance of anterior pituitary and the mechanism involved *Proc Soc Exper Biol & Med* 30 901 903 (Apr) 1933
- 26 — Exophthalmos of Graves disease Its experimental production and significance *Am J M Sc* 188 565 571 (Oct) 1934
- 27 Marx W Magy D B Simpson M E and Evans H M Effect of purified pituitary preparations on urine nitrogen in rat *Am J Physiol* 137 544 550 (Oct) 1942
- 28 Paulson D L Experimental exophthalmos in the guinea pig *Proc Soc Exper Biol & Med* 36 604 605 (June) 1937
- 29 Phillips R A and Robb P D Metabolism studies in albino rat carbohydrate studies after hypophysectomy *Endocrinology* 25 187 192 (Aug) 1939
- 30 Pugsley L I The effect of thyrotropic hormone upon serum cholesterol *Biochem J* 29 513 516 1935
- 31 Pugsley L I and Anderson E M The effect of the growth and thyrotropic hormones of the anterior pituitary upon the calcium metabolism of the rat *Am J Physiol* 109 85 (July) 1934
- 32 Pugsley L I Anderson E M and Collip J II The effect of thyrotropic hormone and of desiccated thyroid upon creatine and creatinine excretion *Biochem J* 28 1135 1140 1934
- 33 Rawson R W Stone II and Aub J C Physiological reactions of the thyroid stimulating hormone of the pituitary *Tr Am Assn for Study of Goiter* pp 159 168 1941

- 4 Carreyett R A, Golts Y M and Reiss M Action of gonadotropic hormone and of pituitary corticotrophic hormone on cholesterol content of adrenals *J Physiol* 104 210 214 (Oct) 1945
- 5 Casida L E Production of ovulation by gonadotropic extracts *Endocrinology* 18 714 720 (Nov-Dec) 1934
- 6 Chow B F, Greep R O and van Dyke H B Effects of digestion by proteolytic enzymes on gonadotropic and thyrotrophic potency of anterior pituitary extract *J Endocrinol* 1 440-469 (Dec) 1939
- 7 Cutuly E Effects of luteogenic and gonadotropic hormones on hypophysectomized pregnant rats *Endocrinology* 31 13 22 (July) 1942
- 8 Evans H M, Meyer K and Simpson M E Growth and Gonad Stimulating Hormones of Anterior Hypophysis pp 155 and 207 Berkeley Univ California Press 1933
- 9 Evans H M, Simpson M E and Lyons W R Influence of luteogenic preparations on production of traumatic placentoma in rat *Proc Soc. Exper Biol & Med* 46 586 590 (Apr) 1941
- 10 Evans H M, Simpson M E, Lyons W R and Turpeinen K Anterior pituitary hormones which favor production of traumatic uterine placentomata *Endocrinology* 28 933 945 (June) 1941
- 11 Evans H M, Simpson M E and Turpeinen K Stimulation of deciduomata around threads on administration of luteogenic and adrenocorticotrophic hormones (Abstr) *Anat Rec* 70 26 (Apr) 1938
- 12 Fevold H L Sex and Internal Secretions pp 966 995 Baltimore Williams & Wilkins 1939
- 13 — Functional synergism of the follicle stimulating and luteinizing hormones of the pituitary (Suppl 2) *Anat Rec* 73 19 (Apr) 1939
- 14 — Chemical differences of follicle stimulating and luteinizing hormones of pituitary *J Biol Chem* 128 83 92 (Apr) 1939
- 15 — Synergism of follicle stimulating and luteinizing hormones in producing estrogen secretion *Endocrinology* 22 33 36 (Jan) 1941
- 16 Foster M A Differential action of pituitary gonadotropic hormones upon secretory capacity of graafian follicle and corpus luteum *Am J Physiol* 121 633 639 (Mar) 1938
- 17 Foster M A and Fevold H L Interrelationship of pituitary gonadotropic hormones in follicular development and ovulation of juvenile rabbit *Am J Physiol* 121 625 632 (Mar) 1938
- 18 Foster M A, Foster R C and Hisaw F L Interrelationship of pituitary sex hormones in ovulation corpus luteum formation and corpus luteum secretion in hypophysectomized rabbit *Endocrinology* 21 249 259 (Mar) 1937
- 19 Fraenkel Conrat H, Li C H and Simpson M E Essays in Biology p 185 Berkeley Univ California Press 1943
- 20 Greep R O Effects of follicle stimulating and luteinizing hormones on the testicles and accessories of normal and hypophysectomized rats *Anat Rec* 64 55 1935
- 21 — Effect of gonadotropic hormones on persisting corpora lutea in hypophysectomized rats *Endocrinology* 23 154 163 (Aug) 1938
- 22 Greep R O, Fevold H I and Hisaw F L Effects of two hypophyseal gonadotropic hormones on the reproductive system of the male rat *Anat Rec* 65 261 271 (June) 1936
- 23 Greep R O and Fevold H L The permatogenic and secretory function of the gonads of hypophysectomized adult rats treated with pituitary FSH and LH *Endocrinology* 21 611 618 (Sept) 1937
- 24 Greep R O, Van Dyke H B and Chow B F Separation in nearly pure form of luteinizing (interstitial cell stimulating) and follicle stimulating (gametogenic) hormones of the pituitary gland *J Biol Chem* 133 289 290 (Feb) 1940
- 25 — Gonadotropins of swine pituitary various biological effects of purified thyliaketrin (FSH) and pure metaketrin (ICSH) *Endocrinology* 30 635 649 (May) 1942
- 26 Hertz R and Hisaw F L Effects of follicle stimulating and luteinizing pituitary extracts on the ovaries of the infantile and juvenile rabbit *Am J Physiol* 108 1 13 1934
- 27 Hisaw F L Development of the graafian follicle and ovulation *Physiol Rev* 27 95 120 (Jan) 1947
- 28 Li C H, Simpson M E and Evans H M Interstitial cell stimulating hormone method of preparation and some physico chemical studies *Endocrinology* 27 803 808 (Nov) 1940
- 29 Lyons W R, Simpson M E and Evans H M Hormonal requirements for pregnancy and mammary development in hypophysectomized rats *Proc Soc Exper Biol & Med* 52 134 136 (Feb) 1943
- 30 Marx W, Magy H B, Simpson M E and Evans H M Effect of purified pituitary preparations on urine nitrogen in rat *Am J Physiol* 137 544 550 (Oct) 1942
- 31 McCullagh D R, and Bowman W E Excretion and assay of gonadotropic hormones from human male urine *Endocrinology* 27 525 526 (Sept) 1940
- 32 Reifstein E C Jr, Forbes A F, Albright F and Donaldson F Effects of methyl testosterone on urinary 17 ketosteroids of adrenal origin *J Clin Investigation* 24 416-434 (July) 1945
- 33 Reiss M Influence of the pituitary anterior lobe upon the specific dynamic action of protein *J Endocrinol* 2 329 338 (Aug) 1940
- 34 Schure I and Sharpey Schaefer E P Observations on pituitary control of creatine and creatinine excretion *Clin Sc* 3 369 376 (Dec) 1938
- 35 Shedlovsky T, Rothen R, Greep R O, Van Dyke H B and Chow B F Isolation in pure form of interstitial cell stimulating (luteinizing) hormone of anterior lobe of pituitary gland *Science* 62 178 180 (Aug) 1940
- 36 Simpson M E, Li C H and Evans H M Biological properties of pituitary interstitial cell stimulating hormone (ICSH) *Endocrinology* 30 969 976 (June) 1942
- 37 Tobin C E Effects of luteogen on normal and adrenalectomized female rats *Endocrinology* 31 197 200 (Aug) 1942
- 38 Whicher C H and Watson E M Effects of thyrotrophic hormone gonadotropic factor pituitary growth substance and insulin upon phosphatase content of rat femurs *Endocrinology* 33 83 86 (Aug) 1943
- 39 Zalesky M, Wells L J, Overholser M D and Gomez E T Effects of hypophysectomy and replacement therapy on thyroid and adrenal

glands of male ground squirrel *Endocrinology* 28 521 530 (Apr) 1941

B Individual Hormones

5 Thyrotropic Hormone (TSH)

- 1 Aird H B Experimental exophthalmos and associated myopathy induced by thyrotropic hormone *Ann Int Med* 15 564 581 (Sept) 1941
- 2 Albert A Experimental production of exophthalmos in *Fundulus* by means of anterior pituitary extracts *Endocrinology* 37 389 406 (Dec) 1945
- 3 Anderson E M and Collip J B Thyrotropic hormone of anterior pituitary *Proc Soc Exper Biol & Med* 30 680 683 (Feb) 1933
- 4 Aron M Action de la hypophyse sur la thyroïde chez la cobaye *Compt rend Soc de biol* 102 682 684 (Nov) 1929
- 5 — Particularités histologiques de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse *Compt rend Soc de biol* 103 145 147 (Jan) 1930
- 6 Baumann E J and Marne D Glycosuria in rabbits following injections of saline extract of anterior pituitary *Proc Soc Exper Biol & Med* 29 1220 1223 (June) 1932
- 7 Benedict E B Putnam T J and Teel H M Early changes produced in dogs by the injection of a sterile active extract from the anterior lobe of the hypophysis *Am J M Sc* 179 489 497 (Apr) 1930
- 8 Buhler F Tierexperimentelle Untersuchungen über den Einfluss von verschiedenen Hormonen auf die Ausscheidung von Kreatin und Kreatinin im Urin *Ztschr f d ges exper Med* 96 821 844 1935
- 9 Closs K, Loeb L and Mackay E The effect of an acid extract of the anterior pituitary on the iodine concentration of the blood and thyroid gland *J Biol Chem* 96 585 597 (June) 1932
- 10 Dobyns B M Studies on exophthalmos produced by thyrotropic hormone study of exophthalmos produced by various thyrotropic hormones and influence of testes on exophthalmos *Surg Gynec & Obst* 82 290-300 (Mar) 1946
- 11 — Studies on exophthalmos produced by thyrotropic hormone changes induced in various tissues and organs (including orbit) by thyrotropic hormone and their relationship to exophthalmos *Surg Gynec & Obst* 82 609 617 (May) 1946
- 12 Eitel H, and Lexer E W Schilddrüsenatagie und Frakturheilung *Arch f klin Chir* 185 587 598 1936
- 13 Foster G L and Smith F E Hypophysectomy and replacement therapy in relation to basal metabolism and specific dynamic action in rat *J A M A* 87 2151 2153 (Dec) 1926
- 14 Fraenkel Conrad J Fraenkel Conrad H and Evans H M Effects of purified pituitary preparations on nonprotein nitrogen constituents of blood *Am J Physiol* 137 200 212 (Aug) 1942
- 15 Fraenkel Conrad H L Simpson M E and Evans H M Effect of purified pituitary preparations on liver weights of hypophysectomized rats *Am J Physiol* 135 398-403 (Oct) 1941
- 16 Friedgood H E Experimental exophthalmos and hyperthyroidism in guinea pigs *Bull Johns Hopkins Hosp* 54 48 73 (Jan) 1934
- 17 Hogben L T Studies on internal secretion I The effect of pituitary (anterior lobe) injection upon normal and thyroidectomized axolotls *Proc Roy Soc London s B* 94 204 215 (Jan) 1933
- 18 Housay H A Blasotti A and Maldonado A Hipofisis y tiroidea acción del extracto del lóbulo anterior de la hipófisis sobre la histología de la tiroidea del perro *Rev Soc argent de biol* 8 130 143 (May June) 1932
- 19 Loeb L and Bassett R B Effect of hormones of anterior pituitary on thyroid gland in the guinea pig *Proc Soc Exper Biol & Med* 26 860 862 (June) 1929
- 20 — Comparison of effects of various preparations of anterior pituitary gland on thyroid of guinea pig *Proc Soc Exper Biol & Med* 27 490-492 (Mar) 1930
- 21 Loeb L, Bassett R B and Friedman H Further investigation concerning the stimulating effect of anterior pituitary gland preparation on the thyroid gland *Proc Soc Exper Biol & Med* 28 709 713 (Dec) 1930
- 22 Loeb L and Friedman H Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle *Proc Soc Exper Biol & Med* 29 648 650 (Feb) 1932
- 23 Marne D Studies on pathological physiology of exophthalmos of Graves disease *Ann Int Med* 12 443 453 (Oct) 1938
- 24 Marne D and Rosen S H Effect of thyrotropic hormone on auto and heterotransplants of thyroid and its bearing on question of secretory nerves *Am J Physiol* 107 677 680 (Mar) 1934
- 25 — Exophthalmos in thyroidectomized guinea pigs by thyrotropic substance of anterior pituitary and the mechanism involved *Proc Soc Exper Biol & Med* 30 901 903 (Apr) 1933
- 26 — Exophthalmos of Graves disease Its experimental production and significance *Am J M Sc* 188 565 571 (Oct) 1934
- 27 Marx W Mary D B Simpson M E and Evans H M Effect of purified pituitary preparations on urine nitrogen in rat *Am J Physiol* 137 544 550 (Oct) 1942
- 28 Paulson D L Experimental exophthalmos in the guinea pig *Proc Soc Exper Biol & Med* 36 604 605 (June) 1937
- 29 Phillips R A and Robb P D Metabolism studies in albino rat carbohydrate studies after hypophysectomy *Endocrinology* 25 187 192 (Aug) 1939
- 30 Pugsley L I The effect of thyrotropic hormone upon serum cholesterol *Biochem J* 28 513 516 1935
- 31 Pugsley L I and Anderson E M The effect of the growth and thyrotropic hormones of the anterior pituitary upon the calcium metabolism of the rat *Am J Physiol* 109 85 (July) 1934
- 32 Pugsley L I Anderson E M and Collip J B The effect of thyrotropic hormone and of desiccated thyroid upon creatine and creatinine excretion *Biochem J* 28 1135 1140 1934
- 33 Rawson R W Stone G H and Aub J C Physiological reactions of the thyroid stimulating hormone of the pituitary *Tr Am Assn for Study of Gaster* pp 159 168 1941

- 34 Reiss M Influence of the pituitary anterior lobe upon the specific dynamic action of protein *J Endocrinol* 2 329-338 (Aug) 1941
- 35 Riddle H and Polhemus I Studies on the physiology of reproduction in birds XXXI Effects of anterior pituitary hormones on gonads and other organ weights in the pigeon *Am J Physiol* 121 130 (Aug) 1931
- 36 Schittenhelm A and Eisler H Der Blutjodspiegel in seiner pathologisch-physiologischen und klinischen Bedeutung *Klin Wochenschr* 11 6-9 (Jan) 1932
- 37 Schockaert J A Enlargement and hyperplasia of the thyroids in the young duck from the injection of anterior pituitary *Am J Anat* 49 3 9-408 (Jan) 1932
- 38 Schockaert J A and Foster G L Influence of anterior pituitary substances on the total iodine content of the thyroid gland in the young duck *J Biol Chem* 95 89 94 (Feb) 1932
- 39 Schreier I and Sharpey-Schafer E P Observations on pituitary control of creatine and creatinine excretion *Can Sci* 3 369 376 (Dec) 1938
- 40 Siebert W J and Smith R S Effect of various anterior pituitary preparations on basal metabolism in guinea pigs *Proc Soc Exper Biol & Med* 27 622-624 (Apr) 1930
- 41 — The effect of various anterior pituitary preparations upon basal metabolism in partially thyroidectomized and in completely thyroidectomized guinea pigs *Am J Physiol* 95 396 40 (Nov) 1930
- 42 Smelser G E Experimental production of exophthalmos resembling that found in Graves disease *Proc Soc Exper Biol & Med* 35 128 130 (Dec) 1936
- 43 — Comparative study of experimental and clinical exophthalmos *Am J Ophthalm* 20 1189 1203 (Dec) 1937
- 44 — Treatment of experimentally produced exophthalmos with thyroxine and other iodine compounds *Am J Ophthalm* 21 1208 1218 (Nov) 1938
- 45 — Histology of orbital and other fat tissue deposits in animals with experimentally produced exophthalmos *Am J Path* 15 341 352 (May) 1939
- 46 Spaul E A Experiments on the injection of pituitary body (anterior lobe) extracts to axolotls *Brit J Exper Biol* 2 33 55 (Dec) 1924
- 47 Turner K B and Delamater A Effect of thyrotropic hormone on blood cholesterol of thyroidectomized rabbits *Proc Soc Exper Biol & Med* 49 150 152 (Feb) 1942
- 48 Uhlenhuth E and Schwartzbach H Hypophysis and thyroid gland *Proc Soc Exper Biol & Med* 26 149 154 (Nov) 1928
- 49 Whicher C H and Watson E M Effects of thyrotropic hormone gonadotropic factor pituitary growth substance and insulin upon phosphatase content of rat femurs *Endocrinology* 23 81 86 (Aug) 1943
- 50 Young F G Identity and mechanism of action of glycotropic (anti insulin) substance of anterior pituitary gland *Biochem J* 32 1521 1539 (Sept) 1938
- 51 Zunz E and LaBarre J Contributions à l'étude des variations physiologiques de la sécrétion interne du pancréas *Arch Internat de physiol* 42 95 110 (Oct) 1935
- B Individual Hormones**
- 6 Adrenocorticotrophic Hormone (corticotrophic adrenotropic ACTH)**
- 1 Albright F Cushing's syndrome its pathological physiology its relationship to adrenal genital syndrome and its connection with problem of reaction of body to injurious agents (alarm reaction of Selye) *Harvey Lect* (1942 1943) 22 123 186 1943
- 2 Albright F, Reifenstein E C and Forbes A P Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 12th Meeting Feb 4 5 New York Josiah Macy Jr Foundation 1946 p 23
- 3 Anderson E Page W L C H., and Ogden E Restoration of renal hypertension in hypophysectomized rats by administration of adrenocorticotrophic hormone *Am J Physiol* 141 393 396 (May) 1944
- 4 Baker H L and Ingle D J Growth inhibition in bone and bone marrow following treatment with ACTH *Endocrinology* 43 422-429 (Dec) 1948
- 5 Becks H, Simpson M F., Li C H., and Evans H M Effects of adrenocorticotrophic hormone (ACTH) on osseous system in normal rats *Endocrinology* 34 305 310 (May) 1944
- 6 Becks H Simpson M E Marx W Li C H., and Evans H M Antagonism of pituitary adrenocorticotrophic hormone (ACTH) to action of growth hormone on osseous system of hypophysectomized rats *Endocrinology* 34 311 316 (May) 1944
- 7 Carreyet, R A Golla Y M and Reels M Action of gonadotrophic hormone and of pituitary corticotrophic hormone on cholesterol content of adrenals *J Physiol* 104 210-214 (Oct) 1945
- 8 Conn J W Louis L H and Johnston M W Studies upon mechanisms involved in the induction with adrenocorticotrophic hormone of temporary diabetes in man *Proc Am Diabetes A* 8 213 239 1948
- 9 Dougherty T F Chae J H., and White W Relationship of the effects of adrenal cortical secretion on lymphoid tissue and on antibody titer *Proc Soc Exper Biol & Med* 56 28 29 (May) 1944
- 10 Dougherty T F and White A Effect of pituitary adrenotropic hormone on lymphoid tissue *Proc Soc Exper Biol & Med* 53 132 133 (June) 1943
- 11 — Influence of hormones on lymphoid tissue structure and function Role of pituitary adrenotropic hormone in regulation of lymphocytes and other cellular elements of blood *Endocrinology* 35 1 14 (July) 1944
- 12 — Influence of adrenal cortical secretion on blood elements *Science* 98 367 369 (Oct) 1943
- 13 — Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 6th Meeting Feb 11 12 New York Josiah Macy Jr Foundation 1944 pp 71 75
- 14 — Evaluation of alterations produced in lymphoid tissues by pituitary adrenal cortical secretion *J Lab & Clin Med* 32 584 604 (June) 1947
- 15 Emery F M and Atwell W J Hypertrophy of the adrenal glands following administration of pituitary extract *Anat Rec* 58 17 24 (Dec.) 1933

- 16 Evans H M, Simpson M E and Li C H Inhibiting effect of adrenocorticotrophic hormone on growth of male rats *Endocrinology* 33 237-238 (Oct.) 1943
- 17 Forsham P H, Prunty F T G and Thorn H W Urinary urea and creatinine ratio following administration of pituitary adrenocorticotrophic hormone (ACTH) as a simple test for adrenal cortical function *J Clin Endocrinol* 7 459 (June) 1947
- 18 Forsham P H, Thorn G W, Prunty F T G and Hills A G Clinical studies with pituitary adrenocorticotropin *J Clin Endocrinol* 8 15-66 (Jan.) 1948
- 19 Fraenkel Conrat H, and Evans H M Increased liver arginase on administration of adrenocortical and corticotrophic hormones *Science* 95 305-306 (Mar.) 1942
- 20 Fraenkel Conrat H, Herring V V, Simpson M E and Evans H M Effect of adrenocorticotrophic hormone on insulin content of rats' pancreas *Proc Soc Exper Biol & Med* 55 62-63 (Jan.) 1944
- 21 Fraenkel Conrat H, Simpson M E and Evans H M Effect of hypophysectomy and of purified pituitary hormones on liver arginase activity of rats *Am J Physiol* 138 439-449 (Feb.) 1943
- 22 — Influence of adrenalectomy and of adrenocortical steroids on liver arginase *J Biol Chem* 147 99-108 (Jan.) 1943
- 23 — Effect of hypophysectomy and of purified pituitary hormones on liver arginase activity of rats *Am J Physiol* 138 439-449 (Feb.) 1943
- 24 Fraenkel Conrat J, Fraenkel Conrat H and Evans H M Effects of purified pituitary preparations on nonprotein nitrogen constituents of blood *Am J Physiol* 137 200-212 (Aug.) 1942
- 25 Fredgood H B The effect of an alkaline extract of the anterior hypophysis upon the weight of the spleen and adrenal glands and upon the blood calcium level *Endocrinology* 20 139-140 (Mar.) 1936
- 26 Gomez E T and Turner C W The adrenotropic principle of the pituitary in relation to lactation *Proc Soc Exper Biol & Med* 36 78-80 (Feb.) 1937
- 27 Gordon G M, Li C H and Bennett L L Effect of adrenocorticotrophic hormone on urinary nitrogen excretion in the normal rat *Proc Soc Exper Biol & Med* 62 103-105 (June) 1946
- 28 Grattan J F and Jen en H Effect of pituitary adrenocorticotrophic hormone and of various adrenal cortical principles on ulnar hypoglycemia and liver glycogen *J Biol Chem* 135 511-517 (Sept.) 1940
- 29 Herbert P H and De Vries J A The administration of ACTH to normal human subjects *Endocrinology* 44 259-273 (Mar.) 1949
- 30 Herring V V and Evans H M Effects of purified anterior pituitary hormones on carbohydrate stores of hypophysectomized rats *Am J Physiol* 140 452-459 (Dec.) 1943
- 31 Hills A G, Forsham P H and Finch C A Changes in circulating leukocytes induced by pituitary adrenocorticotrophic hormone in man *J Clin Endocrinol* 7 458 (June) 1947
- 32 Howay B A, Biasotti A, Mazzuolo P and Sammartino R Action de l'extrait antero hypophysaire sur les surrénales *Compt. rend. Soc de biol* 114 737-739 (Aug.) 1933
- 33 Hume D H The role of the hypothalamus in the pituitary-adrenal cortical response to stress (Abstract) *J Clin Investigation* 28 790 (July) 1949
- 34 Ingle D J, and Barker H L Growth inhibition in bone and bone marrow following treatment with adrenocorticotropin (ACTH) *Endocrinology* 43 422-429 (Dec.) 1943
- 35 Ingle H J, Hargins G M and Kendall E C Atrophy of adrenal cortex in rat produced by administration of large amounts of cortin *Anat Rec* 71 363-372 (July) 1938
- 36 Ingle D J, Li C H, and Evans H M The effect of adrenocorticotrophic hormone on urinary excretion of sodium chloride potassium nitrogen and glucose in normal rats *Endocrinology* 39 32-42 (July) 1946
- 37 Ingle D J, Prestrud M C and Li C H Further study of essentiality of adrenal cortex in mediating metabolic effects of adrenocorticotrophic hormone *Endocrinology* 43 207-207 (Oct.) 1948
- 38 Jen en H and Grattan J F Identity of glycotropic (anti insulin) substance of anterior pituitary gland *Am J Physiol* 128 240-275 (Jan.) 1940
- 39 Jensen H, Grattan J F, and Hart G W Study on peculiarity of anti insulin effect *Endocrinology* 30 203-207 (Feb.) 1942
- 40 Kendall E C Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 10th Meeting June 15-16 New York Josiah Macy Jr Foundation 1945 pp 81-97
- 41 — The chemistry and partial synthesis of adrenal steroids *Ann New York Acad Sc* 50 340-347 (June) 1949
- 42 Koneff A A Effect of adrenocorticotrophic hormone on anterior pituitary of normal young male rat *Endocrinology* 34 77-82 (Feb.) 1944
- 43 Li C H, Kalman C, Evans H M and Simpson M E The effect of hypophysectomy and adrenocorticotrophic hormone on the alkaline phosphatase of rat plasma *J Biol Chem* 163 715-721 (June) 1946
- 44 Li C H, Simpson M E and Evans H M Isolation of adrenocorticotrophic hormone from sheep pituitaries *Science* 95 450 (Nov.) 1942
- 45 — Influence of growth and adrenocorticotrophic hormones on the body composition of hypophysectomized rats *Endocrinology* 44 71-75 (Jan.) 1949
- 46 Long C N H Recent Progress in Hormone Research Vol I p 99 New York Acad Press 1947
- 47 Mason H L, Power M H, Rynearson E H, Caramelli L C, Li C H and Evans H M Results of administration of anterior pituitary adrenocorticotrophic hormone to normal human subject *J Clin Endocrinol* 8 114 (Jan.) 1948
- 48 Moon H D Inhibition of somatic growth in castrate rats with pituitary extracts *Proc Soc Exper Biol & Med* 37 34-36 1937
- 49 Nelson W O and Gaunt R Adrenals and pituitary in initiation of lactation *Proc Soc Exper Biol & Med* 36 136-138 (Mar.) 1937
- 50 Pencharz R I and Lyons W R Induced postpartum lactation in hypophysectomized

- 34 Reiss, M.: Influence of the pituitary anterior lobe upon the specific dynamic action of protein. *J Endocrinol* 2 329-338 (Aug.) 1941
- 35 Riddle O and Polhemus I: Studies on the physiology of reproduction in birds. XXXI Effects of anterior pituitary hormones on gonads and other organ weights in the pigeon. *Am J Physiol* 98 121-130 (Aug.) 1931
- 36 Schittenhelm A., and Eisler B.: Der Blutjodspiegel in seiner pathologisch-physiologischen und klinischen Bedeutung. *Klin Wchnschr* 11 6-9 (Jan.) 1932
- 37 Schockaert J A: Enlargement and hyperplasia of the thyroids in the young duck from the injection of anterior pituitary. *Am J Anat* 49 379-408 (Jan.) 1932
- 38 Schockaert J A and Foster G L: Influence of anterior pituitary substances on the total iodine content of the thyroid gland in the young duck. *J Biol. Chem* 88 89-94 (Feb.) 1932
- 39 Schrire I and Sharpey Schafer E P: Observations on pituitary control of creatine and creatinine excretion. *Clin. Sc.* 3 369-376 (Dec.) 1938
- 40 Siebert W J and Smith R S: Effect of various anterior pituitary preparations on basal metabolism in guinea pigs. *Proc. Soc. Exper. Biol. & Med* 27 622-624 (Apr.) 1930
- 41 —: The effect of various anterior pituitary preparations upon basal metabolism in partially thyroidectomized and in completely thyroidectomized guinea pigs. *Am J Physiol* 93 396-402 (Nov.) 1930
- 42 Smelser G M: Experimental production of exophthalmos resembling that found in Graves disease. *Proc. Soc. Exper. Biol. & Med* 33 128-130 (Dec.) 1936
- 43 —: Comparative study of experimental and clinical exophthalmos. *Am J Ophth* 20 1189-1203 (Dec.) 1937
- 44 —: Treatment of experimentally produced exophthalmos with thyroxin and other iodine compounds. *Am J Ophth* 21 1208-1218 (Nov.) 1938
- 45 —: Histology of orbital and other fat tissue deposits in animals with experimentally produced exophthalmos. *Am J Path* 15 341-352 (May) 1939
- 46 Spaul E A: Experiments on the injection of pituitary body (anterior lobe) extracts to axolotls. *Brit J Exper Biol* 2 33-55 (Dec.) 1924
- 47 Turner K B., and Delamater A: Effect of thyrotropic hormone on blood cholesterol of thyroidectomized rabbits. *Proc Soc Exper Biol & Med* 49 150-152 (Feb.) 1942
- 48 Uhlenhuth E and Schwartzbach M: Hypophysis and thyroid gland. *Proc Soc Exper Biol & Med* 26 149-154 (Nov.) 1928
- 49 Whitcher C H and Watson M M: Effects of thyrotropic hormone gonadotropic factor pituitary growth substance and insulin upon phosphatase content of rat femurs. *Endocrinology* 33 83-88 (Aug.) 1943
- 50 Young F G: Identity and mechanism of action of glycotropic (anti insulin) substance of anterior pituitary gland. *Biochem J* 32 1521-1539 (Sept.) 1938
- 51 Zunz E and LaBarre J: Contributions à l'étude des variations physiologiques de la sécrétion interne du pancréas. *Arch Internat de physiol* 21 95-110 (Oct.) 1935
- B Individual Hormones**
- 6 Adrenocorticotrophic Hormone (corticotrophic adrenotropic ACTH)**
- 1 Albright F: Cushing's syndrome its pathological physiology its relationship to adrenal genital syndrome and its connection with problem of reaction of body to injurious agents (alarm reaction) of Selye. *Harvey Lect* (1942-1943) 38 123-186 1943
- 2 Albright F., Reifenstein E C and Forbes A P: Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing. 12th Meeting Feb 4-5 New York Josiah Macy Jr Foundation 1946 p 23
- 3 Anderson E., Page E W., Li C H., and Ogden E: Restoration of renal hypertension in hypophysectomized rats by administration of adrenocorticotrophic hormone. *Am J Physiol* 141 393-396 (May) 1944
- 4 Baker H L and Ingle D J: Growth inhibition in bone and bone marrow following treatment with ACTH. *Endocrinology* 43 422-429 (Dec.) 1948
- 5 Becks H., Simpson M E., Li C H. and Evans H M: Effects of adrenocorticotrophic hormone (ACTH) on osseous system in normal rats. *Endocrinology* 34 305-310 (May) 1944
- 6 Becks H., Simpson M E., Marx W., Li C H., and Evans H M: Antagonism of pituitary adrenocorticotrophic hormone (ACTH) to action of growth hormone on osseous system of hypophysectomized rats. *Endocrinology* 34 311-316 (May) 1944
- 7 Carreyet R A, Golla Y M and Reuss M: Action of gonadotrophic hormone and of pituitary corticotrophic hormone on cholesterol content of adrenals. *J Physiol* 104 210-214 (Oct.) 1945
- 8 Conn J W., Louis L H and Johnston M W: Studies upon mechanisms involved in the induction with adrenocorticotrophic hormone of temporary diabetes in man. *Proc Am Diabetas A* 8 213-239 1948
- 9 Dougherty T F, Chae J H and White W: Relationship of the effects of adrenal cortical secretion on lymphoid tissue and on antibody titer. *Proc Soc Exper Biol & Med* 56 28-29 (May) 1944
- 10 Dougherty T F and White A: Effect of pituitary adrenotropic hormone on lymphoid tissue. *Proc Soc Exper Biol & Med* 53 132-133 (June) 1943
- 11 —: Influence of hormones on lymphoid tissue structure and function. Role of pituitary adrenotropic hormone in regulation of lymphocytes and other cellular elements of blood. *Endocrinology* 35 1-14 (July) 1944
- 12 —: Influence of adrenal cortical secretion on blood elements. *Science* 98 367-369 (Oct.) 1943
- 13 —: Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing. 6th Meeting Feb 11-12 New York Josiah Macy Jr Foundation 1944 pp 71-75
- 14 —: Evaluation of alterations produced in lymphoid tissues by pituitary adrenal cortical secretion. *J Lab & Clin Med* 32 584-604 (June) 1947
- 15 Emery F E and Atwell W J: Hypertrophy of the adrenal glands following administration of pituitary extract. *Anat Rec.* 58 17-24 (Dec.) 1933

- quotient reducing substances *J Biol Chem* 133 243 259 (Mar) 1940
- 5 Houssay B A, Biasotti A di Benedetto E., and Rietti C T Action de l'extrait antéro hypophysaire sur le diabète phlorhizinique *Compt rend Soc de biol* 112 497 499 (Feb) 1933
 - 6 Long C N Pituitary hormones influencing growth in higher animals *Cold Spring Harbor Symp Quant Biol* 10 91 103 1942
 - 7 — The growth and metabolic hormones of the anterior pituitary *Ann New York Acad Sci* 43 383 426 1943
 - 8 Ogilvie R F Growth in relation to diabetogenic and pancretotropic actions of anterior pituitary extract *J Endocrinol* 4 152 158 (Jan) 1945
 - 9 Young F G Permanent experimental diabetes produced by pituitary (anterior lobe) injections *Lancet* 2 372 374 (Aug) 1937
 - 10 — The influence of anterior pituitary extracts on the glycaemic response to insulin and adrenaline in rabbits *J Physiol* 87 13 (Mar) 1936
 - 11 — Diabetogenic action of crude anterior pituitary extracts *Biochem J* 32 513 523 (Mar) 1938
 - 12 — Studies on fractionation of diabetogenic extracts of anterior pituitary gland *Biochem J* 32 524 533 (Mar) 1938
 - 13 — Experimental investigations on relationship of anterior hypophysis to diabetes mellitus *Proc Roy Soc Med* 31 1305 1316 (Sept) 1938
 - 14 — Growth and diabetogenic action of anterior pituitary preparations *Brit M J* 2 897-901 (Dec) 1941
 - 15 — Growth and diabetogenic action of anterior pituitary preparations: growth and experimental insulin insensitive diabetes *Brit M J* 2 715 718 (Dec) 1944
 - 16 — Growth and diabetes in normal animals treated with pituitary (anterior lobe) diabetogenic extract *Biochem J* 39 515 536 1945
- B Individual Hormones**
- 8 Galactins
 - 1 Astwood E H Regulation of corpus luteum function by hypophysial luteotrophin *Endocrinology* 28 309 320 (Feb) 1941
 - 2 Bates R W, Riddle O, Lahr E L and Schooley J H Aspects of splanchnomegaly associated with the action of prolactin *Am J Physiol* 119 603 609 (July) 1937
 - 3 Bates R W, Riddle O and Lahr E L The mechanism of the antagonistic action of prolactin in adult pigeons *Am J Physiol* 119 610-614 (July) 1937
 - 4 Corner G W Hormonal control of lactation: non effect of corpus luteum: positive action of extracts of hypophysis *Am J Physiol* 95 43 55 (Oct) 1930
 - 5 Cowie A T and Folley S J The role of the adrenal cortex in mammary development and its relation to the mammogenic action of the anterior pituitary *Endocrinology* 40 274 285 (Apr) 1947
 - 6 Dresel I The effect of prolactin on the estrus cycle of nonparous mice *Science* 82 173 (Aug) 1935
 - 7 Evans H M, Simpson M E and Lyons, W R Influence of lactogenic preparations on production of traumatic placenta in rat *Proc. Soc Exper Biol & Med* 46 586 590 (Apr) 1941
 - 8 Evans H M., and Simpson M E Lyons, W R and Turpeinen K. Anterior pituitary hormones which favor production of traumatic uterine placenta *Endocrinology* 28 933 945 (June) 1941
 - 9 Evans H M, Simpson M E and Turpeinen K Stimulation of deciduomata around threads on administration of lactogenic and adrenocorticotrophic hormones (Abstract) *Anat Rec* 70 76 (Apr) 1938
 - 10 Fluhmann C F., and Laqueur H L Action of testosterone and prolactin on corpora lutea of rat *Proc Soc Exper Biol & Med* 54 223 225 (Nov) 1943
 - 11 Gomez E T and Turner C W The adrenergic principle of the pituitary in relation to lactation *Proc. Soc Exper Biol & Med.* 36 78 80 (Feb) 1937
 - 12 — Hypophysectomy and replacement therapy in relation to growth and secretory activity of mammary gland *Univ. Missouri Agr Exper Sta Res Bull.* No 259 p 72 1937
 - 13 Gomez E T, Turner C W., and Reece E P Growth of mammary gland of hypophysectomized guinea pig *Proc Soc Exper Biol & Med* 36 286 (Apr) 1937
 - 14 Gomez E T and Turner C W Further evidence for a mammogenic hormone in the anterior pituitary *Proc Soc Exper Biol & Med* 37 607 609 (Jan) 1938
 - 15 Greep R O van Dyke H B and Chow H F Gonadotropins of swine pituitary various biological effects of purified thyliactrin (FSH) and pure metactrin (ICSH) *Endocrinology* 30 635 649 (May) 1942
 - 16 Lahr E L and Riddle O Temporary suppression of estrous cycles in the rat by prolactin *Proc Soc Exper Biol & Med* 34 880-883 (June) 1936
 - 17 Lewis A A and Turner C W The mammogenic hormones of the anterior pituitary I The duct growth factor *Univ. Missouri Agr Exper Sta Res Bull* No 310 p 72 1939
 - 18 Li C H, Ingle D J, Prestrud M C and Nezamis J H Lack of effect of lactogenic hormone upon organ weights, nitrogen and phosphorus balance and the fat and protein content of liver and carcass in male rats given lactogenic hormone *Endocrinology* 44 454 457 (May) 1949
 - 19 Lyons W R Lobule alveolar mammary growth induced in hypophysectomized rats by injection of ovarian and hypophysial hormones in *Essays in Biology* pp 315 329 Berkeley Univ. California Press 1943
 - 20 Lyons W R, Simpson M E., and Evans H M Influence of lactogenic preparations on mammary glands and time of vaginal opening in young rats *Proc Soc Exper Biol & Med.* 48 634 637 (Dec) 1941
 - 21 Marx W, Magy D E, Simpson M E and Evans H M Effect of purified pituitary preparations on urine nitrogen in rat *Am J Physiol* 137 544 550 (Oct) 1942
 - 22 Mixer J P and Turner C W The mammogenic hormones of the anterior pituitary II The lobule alveolar growth factor *Univ*

- rats *Proc Soc Exper Biol & Med* **38** 388 390 (Apr) 1938
 - 51 Perla D Relation of the hypophysis to the spleen I Effect of hypophysectomy on growth and regeneration of spleen tissue II The presence of a spleen stimulating factor in extracts of anterior hypophysis *J Exper Med* **83** 599 615 (Apr) 1936
 - 52 Pincus H and Hoagland H Steroid excretion and stress of flying *J Aviation Med* **14** 173 193 (Aug) 1943
 - 53 Recant L Hume D M Forsham P H and Thorn C W Studies on the effect of epinephrine on the pituitary adrenocortical system *J Clin Endocrinol* **10** 187 229 (Feb) 1950
 - 54 Reinhardt W O Aron H and Li C H Effect of adrenocorticotrophic hormone on leucocyte picture of normal rats and dogs *Proc Soc Exper Biol & Med* **57** 19 21 (Oct) 1944
 - 55 Reis M Influence of the pituitary anterior lobe upon the specific dynamic action of protein *J Endocrinol* **2** 329 338 (Aug) 1940
 - 56 Russell J A Relationship of anterior pituitary and adrenal cortex in metabolism of carbohydrate *Am J Physiol* **128** 552 561 (Feb) 1940
 - 57 Sayers G Burns T W Tyler F H Jager B V Schwartz T B Smith E L Samuels L T., and Davenport H W Metabolic actions and fate of intravenously administered adrenocorticotrophic hormone in man *J Clin Endocrinol* **9** 593 614 (July) 1949
 - 58 Sayers G and Sayers M A Regulation of pituitary adrenocorticotrophic activity during the response of the rat to acute stress *Endocrinology* **40** 265 273 (Apr) 1947
 - 59 — The pituitary adrenal system *Ann New York Acad Sc* **50** 509 678 (June) 1949
 - 60 Sayers G Sayers M A Fry E G White A., and Long C N Effect of adrenotropic hormone of anterior pituitary on cholesterol content of adrenals with review of literature of adrenal cholesterol *Yale J Biol. & Med* **16** 361 392 (Mar) 1944
 - 61 Sayers G Sayers M A Lewis H L and Long C N Effect of adrenotropic hormone on ascorbic acid and cholesterol content of adrenal *Proc Soc Exper Biol & Med* **55** 238 239 (Apr) 1944
 - 62 Sayers G Sayers M A Liang T Y and Long C N Effect of pituitary adrenotropic hormone on cholesterol and ascorbic acid content of adrenal of rat and guinea pig *Endocrinology* **38** 1 9 (Jan) 1946
 - 63 Sayers G Sayers M A White A and Long C N Effect of pituitary adrenotropic hormone on cholesterol content of rat adrenal glands *Proc Soc Exper Biol & Med* **52** 200 202 (Mar) 1943
 - 64 Schenker V Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 5th Meeting Oct 8 9 New York Josiah Macy Jr Foundation 1943 pp 11 20
 - 65 Selye H The Alarm Reaction, *Cyclopedia of Medicine Surgery and Specialties* pp 15-38 Philadelphia Davis 1940
 - 66 — Syndrome produced by diverse noxious agents *Nature* **138** 32 (July) 1936
 - 67 — Role of hypophysis in pathogenesis of diseases of adaptation *Canad M A J* **50** 426 433 (May) 1944
 - 68 Selye H and Hall C E Production of neoplasia and cardiac hypertrophy in rat by desoxycortico terone acetate overdosage *Am Heart J* **27** 338 344 (Mar) 1944
 - 69 Simpson M F Li C H and Evans H M Absence of renotropic effects on the administration of pure adrenocorticotrophic hormone *Endocrinology* **39** 286 288 (Nov) 1946
 - 70 Simpson M F Li C H Reinhardt W O and Evans H M Similarity of response of thymus and lymph nodes to administration of adrenocorticotrophic hormone in rat *Proc Soc Exper Biol & Med* **54** 135 137 (Oct) 1943
 - 71 Smith P F and Engle E T Experimental evidence regarding the role of the anterior pituitary in the development and regulation of the genital system *Am J Anat* **40** 159 217 (Nov) 1927
 - 72 Swann H H Pituitary adrenocortical relationship *Physiol Rev* **20** 493 521 (Oct) 1940
 - 73 Thorn C W Forsham P H Prunty F T and Hills A H A test for adrenal cortical insufficiency *JAMA* **137** 1005 1009 (July) 1945
 - 74 Tyslowitz R Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 4th Meeting June 11 12 New York Josiah Macy Jr Foundation 1943 p 96
 - 75 Ungar G Endocrine function of spleen and its participation in pituitary adrenal response to stress *Endocrinology* **37** 329 340 (Nov) 1945
 - 76 Wells H B and Kendall E E Influence of corticosterone and C hydroxydehydrocorticosterone (compound E) on somatic growth *Proc Staff Meet., Mayo Clin* **15** 324-328 (May) 1940
 - 77 White A and Dougherty T F Pituitary adrenotropic hormone control of rate of release of serum globulins from lymphoid tissue *Endocrinology* **36** 207 217 (Mar) 1945
 - 78 — Effect of prolonged stimulation of adrenal cortex and of adrenalectomy on numbers of circulating erythrocytes and lymphocytes *Endocrinology* **36** 16 23 (Jan) 1945
 - 79 — Influence of pituitary adrenotropic hormone on lymphoid tissue structure in relation to serum proteins *Proc Soc Exper Biol & Med* **56** 26 27 (May) 1944
 - 80 Volley J M and Baxter J S Some effects of pituitary adrenotropic hormone (path) extract of suprarenal cortex and colchicine on the haemopoietic system *J Anat* **80** 132 138 (July) 1946
- ## H Individual Hormones
- ### 7 Diabetogenic Principle
- 1 Best C H Personal communication
 - 2 Campbell J and Best C H Prolonged diabetes after the administration of extracts of the anterior pituitary gland *Am J Physiol* **123** 30 (July) 1938
 - 3 Evans H M Meyer A Simpson M E and Reichert F L Disturbance of carbohydrate metabolism in normal dogs injected with the hypophyseal growth hormone *Proc Soc Exper Biol & Med* **23** 857 858 (Apr) 1932
 - 4 Greaves J D Freiberg I K and Johns H E Preparation and assay of anterior pituitary fractions rich in ketogenic and respiratory

- 9 — Ketonuria in rats on a fat diet (a) after injections of pituitary (anterior lobe) extract (b) during pregnancy *J Physiol* 69 xix 1930
 - 10 — The excretion of acetone bodies on a fat diet as affected by the injection of pituitary (anterior lobe) extract and by pregnancy *Quart J Pharm & Pharmacol* 6 31 38 (Jan-Mar) 1933
 - 11 Campbell J Method of assaying potency of anterior pituitary extracts which increase liver fat *Endocrinology* 23 692 702 (Dec) 1938
 - 12 Chen G and Geiling E M Antidiuretic effect of posterior pituitary extract in completely and partially hypophysectomized rats *Proc Soc Exper Biol & Med* 52 152 153 (Feb) 1943
 - 13 Conn J W and Louis L Pituitary insulinotropic principle *J Clin Endocrinol* 5 247 258 (July-Aug) 1945
 - 14 Cope O and Marks H P Further experiments on the relation of the pituitary gland to the action of insulin and adrenaline *J Physiol* 115 176 (Sept) 1934
 - 15 Dodds E C Noble R L and Williams P C The pituitary gland and the control of urinary excretion *J Physiol* 91 202 211 1937
 - 16 Harrison H C and Long C N Effects of anterior pituitary extracts in fasted rat *Endocrinology* 26 971 978 (June) 1940
 - 17 Himsworth H P Action of Youngs glycotropic factor of anterior pituitary gland *J Physiol* 92 183 207 (Mar) 1938
 - 18 Himsworth H P and Scott D H Relation of hypophysis to changes in sugar tolerance and insulin sensitivity induced by changes of diet *J Physiol* 91 447 458 (Jan) 1938
 - 19 Houchin O B Influence of anterior pituitary extracts on proteins of liver *Endocrinology* 25 759 767 (Nov) 1939
 - 20 Housay B A Diabetes as a disturbance of endocrine regulation *Am J M Sc* 193 581 606 (May) 1937
 - 21 Houssay H A Fogha V G Smyth F S Rietti C T and Houssay A H Hypophysis and secretion of insulin *J Exper Med* 75 547 566 (May) 1942
 - 22 Houssay H A and Potick D Antagonisme entre l'hypophyse et l'insuline chez le crapaud *Compt rend Soc de biol* 101 940 942 (July) 1929
 - 23 Jensen H and Grattan J F Identity of glycotropic (anti insulin) substance of anterior pituitary gland *Am J Physiol* 128 270 275 (Jan) 1940
 - 24 Liang T Y and Wu S W Über eine hypophysäre humorale Steuerung des Eiweißdepots in der Leber *Chinese J Physiol* 12 125 138 (Sept) 1937
 - 25 Long C N Pituitary hormones influencing growth in higher animals *Cold Spring Harbor Symp Quant Biol* 10 91 103 1942
 - 26 — The growth and metabolic hormones of the anterior pituitary *Ann New York Acad Sc* 43 383 426 1943
 - 27 Marks H P and Young F G Pancreotropic factor of anterior pituitary lobe *Lancet* 2 710 712 (Dec) 1940
 - 28 — Hypophysis and pancreatic insulin *Lancet* 1 493-497 (Mar) 1940
 - 29 Mursky I A Influence of anterior pituitary gland on protein metabolism *Endocrinology* 25 52 56 (July) 1939
 - 30 Nelson J F Antil insulin action of anterior pituitary extracts *Australian J Exper Biol & M Sc* 22 131 133 (June) 1944
 - 31 Ogilvie R F Growth in relation to diabetogenic and pancreotropic actions of anterior pituitary extract *J Endocrinol* 4 152 158 (Jan) 1945
 - 32 Paschke K E Hypophysis in protein metabolism Is the pituitary factor active in protein metabolism identical with the growth hormone? *Endocrinology* 23 368 370 (Sept) 1938
 - 33 Pencharz R I Hopper J Jr and Rynearson H H Water metabolism of the rat following removal of the anterior lobe of the hypophysis *Proc Soc Exper Biol & Med* 34 14 17 (Feb) 1936
 - 34 Raab W Wirkung der blutfettsenkenden Hypophysensubstanz (Lipotrin) am Menschen *Ztschr f d ges exper Med* 88 588 615 1933
 - 35 Richardson K C and Young F G Histology of diabetes induced in dogs by injection of anterior pituitary extracts *Lancet* 1 1098 1101 (May) 1938
 - 36 — The pancreotropic action of anterior pituitary extracts *J Physiol* 91 352 364 (Dec) 1937
 - 37 Richter C P Pituitary gland in relation to water exchange *Proc A Research Nerv & Ment Dis* 17 392-409 1938
 - 38 — The pituitary gland in relation to water exchange in The Pituitary Gland Baltimore Williams & Wilkins 1938 pp 392-409
 - 39 Russell J A Relation of anterior pituitary to carbohydrate metabolism *Physiol Rev* 13 1 27 (Jan) 1938
 - 40 Russell J A and Bennett L L Maintenance of carbohydrate levels in fasted hypophysectomized rats treated with anterior pituitary extracts *Proc Soc Exper Biol & Med* 34 406-409 (May) 1936
 - 41 Shipley R A and Long C N H Studies on the ketogenic activity of the anterior pituitary *Biochem J* 32 2242 2256 (Dec) 1938
 - 42 Werner P Hypophyse und Wasserhaushalt *Wien Arch f inn Med* 118 214 1938
 - 43 White H L and Heinbecker P Pituitary regulation of water exchange in the dog and monkey *Am J Physiol* 118 276 284 (Feb) 1937
 - 44 Young F G The influence of glycotropic pituitary extracts on liver glycogen *J Physiol* 90 200 (May) 1937
 - 45 — Studies on fractionation of diabetogenic extracts of anterior pituitary gland *Biochem J* 32 524 533 (Mar) 1938
 - 46 — Identity and mechanism of action of glycotropic (anti insulin) substance of anterior pituitary gland *Biochem J* 32 1521 1539 (Sept) 1938
 - 47 — Growth and diabetogenic action of anterior pituitary preparations *Brit M J* 2 897 901 (Dec) 1941
- H Individual Hormones**
- 13 Renotropic Factor**
- 1 Selye H Role of hypophysis in pathogenesis of diseases of adaptation *Canad M A J* 50 426 433 (May) 1944
 - 2 Selye H and Hollett C Studies concerning renotropic action of pituitary extracts *J Urol* 53 498 502 (Mar) 1945

- Missouri Agr. Exper. Sta. Res. Bull. No. 383 p. 62 1943
- 21 Nathanon I. T., Fevold H. L., and Jennison D. H. Inhibition of estrous cycle in the rodent with postpartum urine and commercial prolactin. *Proc. Soc. Exper. Biol. & Med.* 36 481 483 (May) 1937
- 22 Nelson W. O., and Gaunt R. Adrenals and pituitary in initiation of lactation. *Proc. Soc. Exper. Biol. & Med.* 36 136 138 (Mar) 1936
- 23 Pencharz R. L., and Lyons W. R. Induced postpartum lactation in hypophysectomized rats. *Proc. Soc. Exper. Biol. & Med.* 38 388 390 (Apr) 1938
- 24 Reiss Max. Lactogenic hormone and fat metabolism. *Endocrinology* 40 294 298 (Apr) 1947
- 25 Riddle Oscar. Prolactin a product of anterior pituitary and the part it plays in vital processes. *Scient. Monthly* 47 97 113 (Aug) 1938
- 26 ——— Lactogenic and mammogenic hormones. *J. A. M. A.* 115 22 6 2281 (Dec) 1940
- 27 Riddle O., Bates R. W., and Dyk, horn S. W. A new hormone of the anterior pituitary. *Proc. Soc. Exper. Biol. & Med.* 39 1211 1212 (June) 1932
- 28 ——— The preparation, identification and assay of prolactin—a hormone of the anterior pituitary. *Am. J. Physiol.* 105 191 216 (July) 1933
- 29 Riddle O., Smith G. C., Bates R. W., Moran C. S., and Lahr E. L. Action of anterior pituitary hormones on basal metabolism of normal and hypophysectomized pigeons and on the paradoxical influence of temperature. *Endocrinology* 20 1 16 (Jan) 1936
- 30 Stricker P., and Grueter F. Action du lobe antérieur de l'hypophyse sur la montée lactée. *Compt. rend. Soc. de biol.* 99 1978 1980 (Jan) 1928
- 31 ——— Recherches expérimentales sur les fonctions du lobe antérieur de l'hypophyse. Influence des extraits du lobe antérieur sur l'appareil genital de la lapine et sur la montée lactée. *Pres. e. méd.* 37 1268 1271 1929
- 32 Turpeinen K. Effect of progesterone and lactogenic hormone upon prolongation of pregnancy in lactating mouse. *Essays in Biology*, pp. 563 570 Berkeley Univ. California Press 1943
- 33 White A., Catchpole H. R., and Long C. N. A crystalline protein with high lactogenic activity. *Science* 86 83 (July) 1937
- 34 Young F. G. Studies on fractionation of dialytogenic extracts of anterior pituitary gland. *Biochem. J.* 32 524 533 (Mar) 1938
- 35 ——— Functions of pituitary gland (anterior lobe). *Practitioner* 154 129 137 (Mar) 1945
- B Individual Hormones**
- 9 Adrenomedullotropic Principle**
- 1 Anselmino K. J., Herold L., and Hoffman F. Über eine weitere adrenaltropische Wirkung des Hypophysenvorderlappens. *Klin. Wchnschr.* 13 1724 (Dec) 1934
- 2 Collip J. H. Demonstration of orally active medullotrophic principle in primary extract of pituitary tissue. *Canad. M. A. J.* 42 2-4 (Jan) 1940
- 3 ——— Physiology of anterior pituitary and note on medullotrophic hormone (Joseph Price oration). *Am. J. Obst. & Gynec.* 39 187 203 (Feb.) 1940
- B Individual Hormones**
- 10 Parathyrotropic Hormone**
- 1 Anselmino K. J., Herold L., and Hoffman F. Über die Wirkung des parathyrotropen Hormons des Hypophysenvorderlappens bei verschiedenen Tierarten. *Ztschr. f. d. ges. exper. Med.* 97 51 59 1935
- 2 Anselmino K. J., Hoffman F., and Herold L. Über die parathyrotropen Wirkung von Hypophysenvorderlappen-extrakten. *Klin. Wchnschr.* 12 1944 (Dec) 1933
- 3 ——— Über die parathyrotropen Wirkung von Hypophysenvorderlappen-extrakten. *Klin. Wchnschr.* 13 45-47 (Jan) 1934
- 4 Cattaneo M. Ricerche sperimentali sull'ormone parathyrotropo del lobo anteriore dell'ipofisi. *Riv. di pat. spec.* 361 3 1938
- 5 Hertz H., and Krane A. Parathyrotropic action of the anterior pituitary: histologic evidence in the rabbit. *Endocrinology* 13 350 360 (May-June) 1934
- 6 Riddle O. and Dotti L. B. Blood calcium in relation to anterior pituitary and sex hormones. *Science* 84 557 559 (Dec) 1936
- B Individual Hormones**
- 11 Splenotropic Principle**
- 1 Perla D. Relation of the hypophysis to the spleen. I. Effect of hypophysectomy on growth and regeneration of spleen tissue. II. The presence of a spleen stimulating factor in extracts of anterior hypophysis. *J. Exper. Med.* 63 599 615 (Apr) 1936
- B Individual Hormones**
- 12 Metabolic Factors**
- 1 Anselmino K. J., and Hoffman F. Das Fettstoffwechselhormon des Hypophysenvorderlappens. I. Nachweis, Darstellung und Eigenschaften des Hormon. *Klin. Wchnschr.* 10 2380 2385 (Dec) 1931
- 2 Anselmino K. J., Herold L., and Hoffman F. Über die pankreatotrope Wirkung von Hypophysenvorderlappen-extrakten. *Klin. Wchnschr.* 12 1245 1247 (Aug) 1933
- 3 Anselmino K. J., and Hoffman F. Die pankreatotrope Substanz aus dem Hypophysenvorderlappen. Über die Darstellung und die Eigenschaften der pankreatotropen Substanz. *Klin. Wchnschr.* 12 1435 1436 (Sept.) 1933
- 4 ——— Über Acetonurie nach Behandlung mit dem Fettstoffwechselhormon des Hypophysenvorderlappens. *Ztschr. f. d. ges. Exper. Med.* 94 305 308 1934
- 5 Barnes H. O., Regan J. F., and Bueno J. G. Is there a specific diuretic hormone in the anterior pituitary? *Am. J. Physiol.* 105 559 561 (Sept.) 1933
- 6 di Benedetto E. Extrakt antéro hypophysaire et résistance à l'insuline. *Compt. rend. Soc. de biol.* 112 499 501 (Feb) 1933
- 7 Best C. H., Campbell J., Hast R. E., and Ham A. W. Effect of insulin and anterior pituitary extract on insulin content of pancreas and histology of islets. *J. Physiol.* 101 17 26 (June) 1942
- 8 Burn J. H., and Ling H. W. The effect of pituitary extract and adrenalin on ketonuria and liver glycogen. *Quart. J. Pharm. & Pharmacol.* 2 1 16 (Jan-Mar) 1929

- 16 Smith P E and Smith I P The function of the lobes of the hypophysis as indicated by replacement therapy with different portions of the ox gland *Endocrinology* 7 579 591 (July) 1923
 - 17 Spaul E A Experiments on the localisation of the substances in pituitary extracts responsible for metamorphic and pigmentary changes in amphibia *Brit J Exper Biol* 2 427 437 (July) 1925
 - 18 Sulzberger M B Pituitary hormone intermediate as active antidiuretic in treatment of diabetes insipidus preliminary report *JAMA* 100 1978 1930 (June) 1933
 - 19 Turner N H Diabetes insipidus treatment with intermedin and pituitrin *Endocrinology* 19 275 283 (Mar) 1935
 - 20 Zondek H and Krohn H Hormon des Zwischenlappens der Hypophyse (Intermedin) I Die Rotfärbung der Eizelle als Testobjekt *Klin Wchnschr* 11 405-408 (Mar) 1932
 - 21 — Hormon des Zwischenlappens der Hypophyse (Intermedin) II Intermedin im Organismus (Hypophyse Gehirn) *Klin Wchnschr* 11 849 853 (May) 1932
 - 22 — Hormon des Zwischenlappens der Hypophyse (Intermedin) III Zur Chemie Darstellung und Biologie des Intermedins *Klin Wchnschr* 11 1293 1298 (May) 1932
- B Individual Hormones**
- IN Vasopressin**
- 1 Abel J J Rouiller C A and Geiling E M Further investigations on the oxytocic pressor diuretic principle of the infundibular portion of the pituitary gland *J Pharmacol & Exper Therap* 22 289 316 (Nov) 1923
 - 2 Alpern D Zur Frage der Wechselbeziehungen zwischen innerer und äusserer Sekretion II Mitt Über den Einfluss einiger Hormone und proteinogener Amine auf die Galleabsonderungsfähigkeit der Leber *Biochem Ztschr* 137 507 516 1923
 - 3 Borchardt L Experimentelles über den Diabetes bei der Akromegalie *Deutsche med Wchnschr* 34 946 947 1908
 - 4 Burgess W W Harvey A M and Marshall E K Jr The site of the antidiuretic action of pituitary extract *J Pharmacol & Exper Therap* 49 237 249 (Oct) 1933
 - 5 Burn J H The relation of pituitary extract (infundibular lobe) to the fall of blood sugar produced by insulin *J Physiol* 57 xxxviii 1923
 - 6 Cascao de Anciao J H Insuline pituitrine et sécrétion gastrique *Compt rend Soc de biol* 95 313 315 (July) 1926
 - 7 Cope O and Marks H P Further experiments on relation of pituitary gland to action of insulin and adrenaline *J Physiol* 83 157 176 (Dec) 1934
 - 8 Corey E L and Britton S W Antagonistic action desoxycorticosterone and post pituitary extract on chloride and water balance *Am J Physiol* 133 511 519 (July) 1941
 - 9 Curtis F R and Pickering J W The action of the post pituitary principles on the blood *Lancet* 2 695 697 (Oct) 1928
 - 10 Dicker S E and Heller H The renal action of posterior pituitary extract and its fractions as analysed by clearance experiments on rats *J Physiol* 104 353 360 (Apr) 1945
 - 11 Dougherty T and White A Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 6th Meeting, Feb 11 12 New York Josiah Mary Jr., Foundation 1944 pp 71 74
 - 12 Ellsworth H C The antagonism between posterior lobe pituitary hormones and insulin *J Pharmacol & Exper Therap* 56 417-470 (Apr) 1936
 - 13 Elmer A W and Scheps M Über die Wirkung des Vasopressins und Oxytocins auf den Blutzucker bei Menschen *Klin Wchnschr* 9 2439 2440 (Dec) 1930
 - 14 Elsom K A Glenn P M and Drossner J L Intubation studies of human small intestine effect of pitressin and of amphetamine (benzedrine) sulphate on motor activity of small intestine and colon *Am J Digest Dis* 6 593 597 (Nov) 1939
 - 15 Engel R McQuarrie I and Ziegler M Untersuchungen über den Mineralhaushalt nach Zufuhr von Hypophysenhinterlappensubstanz *Arch exper Path u Pharmacol* 173 248 259, 1933
 - 16 Essex H E Wegria H Herrick J F and Mann F C Effect of certain drugs on coronary blood flow of trained dog *Am Heart J* 19 554 565 (May) 1940
 - 17 Geiling E M De Lawder A and Rosenfeld M Early changes in the blood chemistry of trained unanesthetized dogs in response to crystalline insulin to pitressin and to pitocin *J Pharmacol & Exper Therap* 42 263 (July) 1931
 - 18 Geiling E M and Eddy, C A The hyperglycemic effect of vasopressin oxytocin and pituitrin *Proc Soc Exper Biol & Med* 21 146 147 (Nov) 1928
 - 19 Geiling E M and Oldham F K Neurohypophysis *JAMA* 116 302 306 (Jan) 1941
 - 20 Gersh I Reabsorption of water during pituitary antidiuresis *J Pharmacol & Exper Therap* 52 231 234 (Oct) 1934
 - 21 Gilman A and Goodman L The secretory response of the posterior pituitary to the need for water conservation *J Physiol* 90 113 123 (July) 1937
 - 22 Griffiths J Q Jr Corbit H O Rutherford R B and Lindauer M A Studies of criteria for classification of arterial hypertension types of hypertension associated with presence of posterior pituitary substance *Am Heart J* 21 77 89 (Jan) 1941
 - 23 Griffiths M Antagonism between insulin and posterior lobe pituitary extract *J Physiol* 100 112 116 (Aug) 1941
 - 24 Grollman A and Geiling E M The cardiovascular and metabolic reactions of man to the intramuscular injection of posterior pituitary liquid (pituitrin) pitressin and pitocin *J Pharmacol & Exper Therap* 45 447-450 (Dec) 1937
 - 25 Gruber C M and Kountz W B Some observations on the effect of pitressin upon the cardiovascular system *J Pharmacol & Exper Therap* 39 435-447 (July) 1930
 - 26 Gruber C M and Robinson P I The influence of pituitary extract vasopressin and oxytocin upon the intact intestine in unanesthetized dogs *J Pharmacol & Exper Therap* 36 203 226 (June) 1929
 - 27 Guthrie J S and Bergen J A The effect of

- 3 Selye H and Jensen H Chemistry of hormones *Am Rev Biochem* 15 347 360 1946
- 4 Selye H Stone H Nielsen K and Leblond C P Studies concerning effects of various hormones upon renal structure *Canad M A J* 52 571 582 (June) 1945
- II Individual Hormones**
- 14 Hepatic and Cardiac Factors
- 1 Selye H Role of hypophysis in pathogenesis of diabetes of adaptation *Canad M A J* 50 426 433 (May) 1944
- B Individual Hormones**
- 15 Hematopoietic Factor
- 1 Flaks J, Hummel I and Zlotnik A Sur l'existence d'une hormone hématopoïétique dans l'hypophyse *Presse méd* 45 1261 1262 (Sept) 1937
- 2 Meyer O O Stewart G E Theunis E W, and Rusch H I Hypophysis and hematopoiesis *Folia haemat* 57 99 109 1937
- II Individual Hormones**
- 16 Specific Metabolic Factor
- 1 Billingsley L W, O'Donovan D K and Collip J B Specific metabolic principle of pituitary *Endocrinology* 24 63 68 (Jan) 1939
- 2 Collip J B Results of recent studies on anterior pituitary hormones (Cameron lecture) *Edinburgh M J* 45 782 804 (Nov) 1938
- 3 ——— Results of recent studies on specific metabolic principle of pituitary gland *Tr A Am Physicians* 54 302 303 1939
- 4 ——— A regulator of metabolism *Lancet* 1 997 998 (Apr) 1939
- 5 ——— Pituitary gland in relation to metabolism *West J Surg* 47 1 3 (Jan) 1939
- 6 ——— Physiology of anterior pituitary and note on medullotrophic hormone (Joseph Price oration) *Am J Obst & Gynec* 39 187 203 (Feb) 1940
- 7 Denstedt O F and Collip J B Studies on the melanophore principle of the pituitary *Am J Physiol* 126 476 (July) 1939
- 8 Dobyns H M Studies on exophthalmos produced by thyrotropic hormone study of exophthalmos produced by various thyrotropic hormones and influence of testes on exophthalmos *Surg Gynec & Obst* 82 290 300 (Mar) 1946
- 9 Feinstein N N and Gordon E B Specific metabolic principle of pituitary *Endocrinology* 27 592 596 (Oct) 1940
- 10 Neufeld A H and Collip J B Thermostability of pituitary extracts in relation to ketogenic activity *Canad M A J* 40 535 536 (June) 1939
- 11 ——— Antagonist to adrenalin hyperglycaemia in pituitary extracts *Canad M A J* 40 537 539 (June) 1939
- 12 O'Donovan M K The influence of pituitary extracts on oxygen consumption *Am J Physiol* 119 381 (June) 1937
- 13 O'Donovan D K and Collip J B Specific metabolic principle of pituitary and its relation to melanophore hormone *Endocrinology* 23 718 734 (Dec) 1938
- 14 Rabinowitch I M Mountford M O'Donovan H K and Collip J B Influence of specific hormone of pituitary on basal metabolism in man *Canad M A J* 40 105 107 (Feb) 1939
- 15 Teague R H Relation of melanophore hormone of pituitary gland to oxygen consumption of rat *Endocrinology* 25 953 961 (Dec) 1939
- 16 ——— Melanophore hormone of pituitary gland and metabolic stimulation *Proc Soc Exper Biol & Med* 40 516-519 (Apr) 1939
- B Individual Hormones**
- 17 Chromatophore Stimulating or Expanding Factor
- 1 Anderson E and Haymaker W Elaboration of hormones by pituitary cells growing in vitro *Proc Soc Exper Biol & Med* 33 313-316 (Nov) 1935
- 2 Atwell W J On the nature of the pigmentation changes following hypophysectomy in the frog *Larva Science* 49 48 50 1939
- 3 Dawes B The melanin content of the skin of *Rana temporaria* under normal conditions and after prolonged light and dark adaptation A photometric study *J Exper Biol* 18 26-49 (Sept) 1940
- 4 Dubois Poulsen A Effets de l'extrait hypophysaire et de l'adrénaline sur les franges de l'épithélium pigmentaire de la rétine de la grenouille *Compt rend Soc de biol* 125 248 249 (May) 1937
- 5 Fisher C The site of formation of the posterior lobe hormones *Endocrinology* 21 19 29 (Jan) 1937
- 6 Geising E M Some aspects of the comparative anatomy and pharmacology of the pituitary gland *Harvey Lect* (1941-1942) 37 269 312 1942
- 7 Hogben L T The pigmentary effector system II A further contribution to the role of pituitary secretion in amphibian colour response *Brit J Exper Biol* 1 249 270 (Jan) 1924
- 8 Hogben L T and Winton F R The pigmentary effector system III Colour response in the hypophysectomized frog *Proc Roy Soc Lond B* 15 13 31 1923
- 9 Holmquist A G Die Einwirkung von Intermedin und thyreotroper Substanz des Hypophysenvorderlappens auf den Gehalt an Adrenalin und Ascorbinsäure in den Nebennieren *Klin Wchnschr* 13 664 666 (May) 1934
- 10 Jores A Untersuchungen über die Funktion des Pigmenthormons im Warmblüterorganismus I Mitt Die Wirkungen des Hormons auf Temperatur und Blutzucker bei intraventrikulärer Injektion beim Kaninchen *Ztschr f d ges exper Med* 97 207 213 1935
- 11 Jores A and Beck H Melanophorenhormon und Nebennieren *Ztschr f d ges exper Med* 94 293 299 1934
- 12 Kleinholz L H The melanophore dispersing principle in the hypophysis of *Fundulus heteroclitus* *Biol Bull* 69 379 390 1935
- 13 Lewis D Lee F C and Astwood E H Some observations on intermedin *Bull Johns Hopkins Hosp* 61 198 209 (Sept) 1937
- 14 Muscio Fournier J C Cervino J M and Conti O Treatment of vitiligo by local injections of melanophore hormone *Endocrinology* 23 513 515 (Mar) 1941
- 15 Noble G K and Bradley H T The relation of the thyroid and the hypophysis to the molting process in the lizard *Hemidactylus brooki* *Biol Bull* 289 293 1933

- lation Quart J Exper Physiol 16 251 280 (Aug) 1926
- 60 Silvette H Influence of post pituitary extract on excretion of water and chlorides by renal tubul. Am J Physiol 128 47 753 (Mar) 1940
 - 61 — Renal response to repeated administration of post pituitary extract Am J Physiol 131 601 605 (Jan) 1941
 - 62 Sodeman W A and Engelhardt H T Renal concentration test employing use of pituitary extracts Response of normal subjects, Proc Soc Exper Biol & Med 46 683 691 (Apr) 1941
 - 63 Thaddeus M and Waly A Zur Frage der Wirkungsweise und des Angriffspunktes der so lierten Hypophysenhinterlappenhormone auf den Kohlehydratstoffwechsel Arch f exper Path u Pharmacol 172 535 550 1933
 - 64 Wischnofsky M Kane A P and Byron C S Influence of pituitrin and epinephrine on action of insulin on blood sugar Am J M Sc 208 361 371 (Sept) 1944
 - 65 Wislicki L Antagonism between posterior pituitary lobe and insulin J Physiol 102 274 280 (Dec) 1943
 - 66 Yanagi K The effect of posterior pituitary preparations upon the colloid osmotic pressure of serum protein water and mineral metabolism of dogs J Pharmacol & Exper Therap 80 23 38 (Jan) 1936
- ### B Individual Hormones
- 19 Oxytocin
 - 1 Allan H and Wiles P The role of the pituitary gland in pregnancy and parturition I Hypophysectomy J Physiol 75 23 28 (May) 1932
 - 2 Buhler F Über den Einfluss der Keimdrüsenhormone auf den Geschlechtsapparat den Thy mus und die Hypophyse infantiler Ratten Ztschr f d ges exper Med 98 151 163 1936
 - 3 Dicker S E and Heller H The renal action of posterior pituitary extract and its fractions as analysed by clearance experiments on rats J Physiol 104 353 360 (Apr) 1945
 - 4 Ellsworth H C The antagonism between posterior lobe pituitary hormones and insulin J Pharm 56 417 420 (Apr) 1936
 - 5 Fraser A M Action of oxytocic hormone of pituitary gland on urine secretion J Physiol 101 236 251 (Aug) 1942
 - 6 Geiling E M De Lawder A and Rosenfeld M Early changes in the blood chemistry of trained unanesthetized dogs in response to crystalline insulin to pitressin and to pitocin J Pharmacol & Exper Therap 42 263 1931
 - 7 Geiling E M and Oldham F K Neurohypophysis JAMA 116 302 306 (Jan) 1941
 - 8 Himwich H E Haynes F W and Fazikas J F Effect of posterior pituitary extracts on the constituents of the blood Am J Physiol 101 711 714 (Sept) 1932
 - 9 Holman D V and Ellsworth H C The hyperglycemic constituent of posterior lobe pituitary extract J Pharmacol & Exper Therap 53 377 384 (Mar) 1935
 - 10 Housay B A and Magenta M A Action des substances rétropituitaires sur le sensibilité à l'insuline des chiens privés d'hypophyse Compt rend Soc de biol 102 429 431 (Nov) 1929
 - 11 Ivy A C Hartman C G, and Koff A Contractions of monkey uterus at term Am J Obst & Gynec 22 388 399 (Sept) 1931
 - 12 Kuschinsky G and Bundschuh H — Über eine diuretische und Kochsalz ausschwemmende Substanz in Hypophysenhinterlappen Präparaten Arch f exper Path u Pharmacol 192 683 690 1939
 - 13 Larson E Effect of posterior pituitary preparations on large intestine of unanesthetized dog J Pharmacol & Exper Therap 72 363 369 (Aug) 1941
 - 14 Melville K I, and Stehle R L The actions of pituitary preparations (posterior lobe) upon the intestines of the dog J Pharmacol & Exper Therap 50 165 173 (Feb) 1934
 - 15 Moir J C Effect of posterior lobe pituitary gland fractions on intact human uterus J Obst & Gynaec Brit Emp 51 181 197 (June) 1944
 - 16 Newton W H The insensitivity of the cervix uteri to oxytocin J Physiol 100 309 315 (Apr) 1937
 - 17 Ott I and Scott J C The action of infundibulin upon the mammary secretion Proc Soc Exper Biol & Med 14 48 49 (Oct) 1910
 - 18 Quigley J P and Barnes B O Action of insulin on motility of gastro intestinal tract antagonistic action of posterior pituitary lobe preparations Am J Physiol 95 71 79 (Oct) 1930
 - 19 Smith P — The non essentiality of the posterior hypophysis in parturition Am J Physiol 99 345 348 (Jan) 1932
 - 20 Wislicki L Antagonism between posterior pituitary lobe and insulin J Physiol 102 274 280 (Dec) 1943

B Individual Hormones

20 Antidiuretic Principle

 - 1 Burgess W W Harvey A M and Marshall E K Jr The role of the antidiuretic action of pituitary extract J Pharmacol & Exper Therap 49 237 249 (Oct) 1933
 - 2 Corey E L and Britton W W Antagonistic action of desoxycorticosterone and post pituitary extract on chloride and water balance Am J Physiol 133 511 519 (July) 1941
 - 3 Gersh I Reabsorption of water during pituitary antidiuretics J Pharmacol & Exper Therap 52 231 234 (Oct) 1934
 - 4 Gilman A and Goodman L The secretory response of the posterior pituitary to the need for water conservation J Physiol 90 113 123 (July) 1937
 - 5 Hare R H Hare K and Phillips D M Renal excretion of chloride by normal and by diabetes insipidus dog Am J Physiol 140 334 348 (Dec) 1943
 - 6 Heller H Effect of hydrogen ion concentration on stability of antidiuretic and vasopressor activities of posterior pituitary extracts J Physiol 96 337 344 (Aug) 1939
 - 7 Murphy D P Contractile response of human uterus to posterior pituitary extract administered at regular intervals during pregnancy study of 32 patients with Lördén toco-graph Surg Gynec & Obst 73 175 180 (Aug) 1941
 - 8 — Contractile response of uterus to posterior pituitary extract during late pregnancy and its relation to duration of labor study of 26

- drugs on different segments of the intestine of man *Surg Gynec & Obst* 63 743 49 (Dec) 1936
- 28 Haselkorn M and Lendle L Untersuchungen über die Wirkungsweise des Teneptiles sowie über das antagonistische Verhalten der Narкотика zur Teneptilwirkung *Arch f exper Path u Pharmacol* 172 501 524 1933
- 29 Heller H Effect of hydrogen ion concentration on stability of antidiuretic and vasopressor activities of posterior pituitary extracts *J Physiol* 96 337 347 (Aug) 1939
- 30 Hees W R and Cundlach R Der Einfluss von Hypophysenextrakt auf die Magensaftsekretion *Pflügers Arch f d ges Physiol* 185 137 140 1930
- 31 Heymans C and Lupo H Action antagoniste de l'insuline et de l'extrait hypophysaire sur les échanges respiratoires *Compt rend Soc de biol* 94 1253 1254 (Mar) 1926
- 32 Humrich H E Haynes F W., and Spiers M A Effect of posterior pituitary extract on plasma concentration and fat content and on blood sugar *Proc Soc Exper Biol & Med* 33 332-333 (Dec) 1930
- 33 Holman M V., and Ellsworth H C The hyperglycemic constituent of posterior lobe pituitary extract *J Pharmacol & Exper Therap* 53 37, 344 (Mar) 1935
- 34 Houssay B A., and di Benedetto E Action hyperglycémante de l'extrait rétrohypophysaire *Compt rend Soc de biol* 114 91 95 1933
- 35 Hynd A and Rotter D L Studies on the metabolism of animals on a carbohydrate free diet IV The effect of pituitrin and pitocin on the distribution of fat and glycogen in the liver and muscles of albino rats *Biochem J* 26 5 8 585 1932
- 36 Isaac S., and Siegel M Therapeutische Versuche mit einer besonderen Fraktion des Hypophysenhinterlappens bei Diabetes insipidus nebst Bemerkungen über ihren Wirkungsmechanismus *Klin Wchnschr* 8 1 00-1,04 (Sept) 1929
- 37 Larson E Effect of posterior pituitary preparations on large intestine of unanesthetized dog *J Pharmacol & Exper Therap* 72 363 369 (Feb) 1941
- 38 Light R U and Bysshe S M The administration of drugs into the cerebral ventricles of monkeys: pituitrin certain pituitary fractions pitocin pitocin histamine acetyl choline and pilocarpine *J Pharmacol & Exper Therap* 47 17 36 (Jan) 1935
- 39 Long M L Hill E and Buschoff F The posterior pituitary hormone in metabolism III The effect of pitressin and pituitrin upon the lipid distribution *Am J Physiol* 102 402-408 (Nov) 1932
- 40 Manchester R C Influence of posterior pituitary extracts on mineral and water exchange in children *Proc Soc Exper Biol & Med* 29 717 719 (Mar) 1933
- 41 McIntyre A R The effects of posterior lobe pituitary preparations upon the concentrations of copper reducing substances in the serum and urine of dogs *Am J Physiol* 109 73 (July) 1934
- 42 McIntyre A R and Sievers H F Some effects of posterior lobe pituitary extract upon the serum and urine of normal dogs *J Pharmacol & Exper Therap* 49 229 236 (Oct) 1933
- 43 McLellan A Response of non gravid human uterus to posterior pituitary extract and its fractions oxytocin and vasopressin *Lancet* I 919 922 (May) 1940
- 44 Melville K I Pressor and oxytocic fractions of posterior pituitary extract Comparative effects on blood pressure and intestinal activity *JAMA* 106 102 105 (Jan) 1936
- 45 Melville K I and Stehle R L The actions of pituitary preparations (posterior lobe) upon the intestines of the dog *J Pharmacol & Exper Therap* 50 165 173 (Feb) 1934
- 46 Moffat W M The effect of pituitrin injections on blood pressure in man *Am J M Sc* 186 254 260 (Dec) 1933
- 47 Voir J C Effect of posterior lobe pituitary gland fractions on intact human uterus *J Obst & Gynaec. Brit Emp* 51 181 197 (June) 1944
- 48 Molitor H., and Puck E P Über die Bedeutung des Gewebswassers für die Wirkung dauersebeeinflussender Arzneimittel I Mitt Der Einfluss von Flüssigkeitsanreicherung auf die Stärke der Pituitrinwirkung *Arch internat de pharmacodyn et de therap* 38 2 9 286 1930
- 49 Murphy D P Contractile response of human uterus to posterior pituitary extract administered at regular intervals during pregnancy study of 32 patients with Lörand tocomograph *Surg Gynec & Obst* 73 175 180 (Aug) 1941
- 50 ——— Contractile response of uterus to posterior pituitary extract during late pregnancy and its relation to duration of labor study of 26 primigravidae with Lörand tocomograph *Am J Obst & Gynec* 42 281 285 (Aug) 1941
- 51 Neufeld A H and Collip J B Effect of pituitary preparations on glycogen stores of the rat *Endocrinology* 28 926 932 (June) 1941
- 52 Oppenheimer A Wirkungsmechanismus der Hypophysenhinterlappeneextrakte am menschlichen Dickdarm *Deutsche med Wchnschr* 57 537 538 (Mar) 1931
- 53 Pasquini R Q and Etala E Determinacion de la capacidad de reabsorcion del tubulo renal por medio de extractos de lobulo posterior de hipofisis (reabsorcion tubular forzada) *Rev Soc argent de biol* 16 161 173 (June) 1940
- 54 Raab W Blutfett und Blutfetteaktionen bei Fettsucht (Lipotrimresistenz) *Zische f d ges exper Med* 94 284 297 1934
- 55 Roos J B Dreyer A B and Stehle R L The cardiac action of pituitary extract (posterior lobe) *J Pharmacol & Exper Therap* 38 461-472 (Apr) 1930
- 56 Quigley J P and Barnes B O Action of insulin on motility of gastro intestinal tract antagonistic action of posterior pituitary lobe preparations *Am J Physiol* 95 7 12 (Oct) 1930
- 57 Schondube W and Kalk H Untersuchungen über den Einfluss der Hypophysenextrakte auf den Magen *Arch f Verdauungskr* 36 227 244 (Dec) 1935
- 58 ——— Untersuchungen über den Einfluss der Hypophysenextrakte auf den Magen *Arch f Verdauungskr* 36 333 352 (Oct) 1936
- 59 Sharpey Schafer E and Macdonald A D The action of extracts of the posterior lobe of the pituitary body on the pulmonary circu

- lipids to thyroidectomy *Endocrinology* 30 794 801 (May) 1942
- 27 — Blood lipids of hypophysectomized thyroidectomized dog *Endocrinology* 30 802 815 (May) 1942
 - 28 Evans H M Meyer K and Simpson M E Growth and Gonad Stimulating Hormones of Anterior Pituitary pp 229 253 277 301 and 409 Berkeley Univ California Press 1933
 - 29 Evans H M and Szwercy O Ovogenesis and the normal follicular cycle in adult mammalia *Mems Univ of California* 9 119 224 (Dec) 1931
 - 30 Finkelstein G Gordon A S and Charipper H A Effect of sex hormones on anemia induced by hemorrhage in rat *Endocrinology* 35 267 277 (Oct) 1944
 - 31 Fontaine T and Veil C Compensatory renal hypertrophy in hypophysectomized rat *Compt rend Soc de biol* 140 159 167 (Mar) 1946
 - 32 Foster G L and Smith P E Hypophysectomy and replacement therapy in relation to basal metabolism and specific dynamic action in the rat *JAMA* 87 2151 2153 (Dec) 1926
 - 33 Fraenkel Conrat H Simpson M E and Evans H M Effect of hypophysectomy and of purified pituitary hormones on liver arginase activity of rats *Am J Physiol* 138 439 449 (Feb) 1943
 - 34 Fukushima S On the influence of the pituitary extract upon the fatty substances in the blood *Jap J M Sc Tr IV Pharmacol* 5 65 66 1931
 - 35 Gaebler O H The specific dynamic action of meat in hypophysectomized dogs *J Biol Chem* 81 41 47 (Jan) 1929
 - 36 Geiling E M Campbell D and Ishikawa Y The effect of insulin on hypophysectomized dogs *J Pharmacol & Exper Therap* 31 247 268 (July) 1927
 - 37 Gerschman R Calcium et phosphore du plasma sanguin des chiens hypophysoprives *Compt rend Soc de biol* 108 494 495 (Oct) 1931
 - 38 Gerschman R and Marenzi A D Acción del extracto alcalino de lobulo anterior de hipofisis sobre las substancias minerales del plasma *Rev Soc argent de biol* 11 500 508 (Oct) 1935
 - 39 Greeley P O Sugar utilization of hypophysectomized rabbits *Endocrinology* 27 317 321 (Aug) 1940
 - 40 Griffiths M Influence of anterior pituitary extracts on insulin content of pancreas of hypophysectomized rat *J Physiol* 100 104 111 (Aug) 1941
 - 41 Haist R E Pituitary and insulin content of pancreas *J Physiol* 98 419 423 (Sept) 1940
 - 42 Haist R E and Best C H Factors affecting insulin content of pancreas *Science* 91 410 (Apr) 1940
 - 43 Hogben L Charles E and Slome D Studies on the pituitary VIII The relation of the pituitary gland to calcium metabolism and ovarian function in *Xenopus* *J Exper Biol* 8 345 354 (Oct) 1931
 - 44 Houssay B A What we have learned from the toad concerning hypophysal functions *New England J Med* 214 913 926 (May) 1936
 - 45 — The hypophysis and metabolism *New England J Med* 214 961 971 (May) 1936
 - 46 — Carbohydrate metabolism *New England J Med* 214 971 986 (May) 1936
 - 47 — Asthenia hypophysopriva *New England J Med* 214 1023 1030 (May) 1936
 - 48 — Hypophysis and blood pressure *New England J Med* 214 1086 1092 (May) 1936
 - 49 — Hypophysis and resistance to intoxication infections and tumors *New England J Med* 214 1137 1146 (June) 1936
 - 50 — Diabetes as a disturbance of endocrine regulation *Am J M Sc* 193 581 606 (May) 1937
 - 51 — Acción de la hipofisis sobre el páncreas y la secreción de insulina *Medicina* 2 205 229 (Jan) 1942
 - 52 Houssay B A di Benedetto E and Mazocco P Hypophyse et glycogène chez le crapaud *Compt rend Soc de biol* 113 465 467 (Apr) 1933
 - 53 Houssay B A and Biasotti A Le diabète pancréatique des chiens hypophysectomisés *Compt rend Soc de biol* 105 121 123 (Oct) 1930
 - 54 — Les troubles diabétiques chez les chiens privés d'hypophyse et de páncreas *Compt rend Soc de biol* 105 124 126 (Oct) 1930
 - 55 — Hypophysectomie et diabète pancréatique chez le crapaud *Compt rend Soc de biol* 104 407 410 (May) 1930
 - 56 — The hypophysis carbohydrate metabolism and diabetes *Endocrinology* 15 511 523 (Nov Dec) 1931
 - 57 Houssay B A Foglia V C and Fustinoni O Intestinal absorption of sugars in toad with hypophysal or adrenal insufficiency *Endocrinology* 28 915 922 (June) 1941
 - 58 Houssay B A Foglia V S Smyth F S Rieth C T and Houssay A B Hypophysis and secretion of insulin *J Exper Med* 75 547 566 (May) 1942
 - 59 Houssay B A and Magenta M A Sensitivity to insulin of dogs after loss of pituitary *Rev Soc argent de biol* 37 389 406 19 4
 - 60 Houssay B A and Potuck D Antagonisme entre l'hypophyse et l'insuline chez le crapaud *Compt rend Soc de biol* 101 940 942 (July) 1929
 - 61 Houssay B A Royer M and Orías O Hemoglobina y globulos rojos en los perros hipofisoprivos *Rev Soc argent de biol* 7 314 319 1931
 - 62 Houssay B A and Sammartino R Modificaciones histológicas de la surrenale chez les chiens hypophysoprives ou a tuber lésé *Compt rend Soc de biol* 114 717 721 (Aug) 1933
 - 63 Huggins C and Russell P S Quantitative effects of hypophysectomy on testes and prostate of dogs *Endocrinology* 39 1 7 (July) 1946
 - 64 Ingle D J Time for occurrence of cortico adrenal hypertrophy in rats during continued work *Am J Physiol* 124 627 630 (Dec) 1938
 - 65 Joseph M Schweizer M Ulmer N Z and Gaunt R Anterior pituitary and its relation to adrenal cortex in water diuresis *Endocrinology* 35 338 346 (Nov) 1944
 - 66 Kobayashi K On the effect of extracts of some endocrine organs on carbohydrate metabolism

- primigravidae with Lóránd tograph Am J Obst & Gynec 42 281 285 (Aug) 1941
- 9 Paine W H and Nelson E E Concentrating capacity of kidney as revealed by injection of posterior pituitary extract Proc Soc Exper Biol & Med 42 729 731 (Dec) 1939
 - 10 Paquahin R Q and Fitala F Determinación de la capacidad de reabsorción del tubulo renal por medio de extractos de lóbulo posterior de hipófisis (reabsorción tubular forzada) Rev Soc argent de biol 16 161 173 (June) 1940
 - 11 Silvette H Influence of post pituitary extract on excretion of water and chlorides by renal tubules Am J Physiol 128 747 753 (Mar) 1940
 - 12 — Renal response to repeated administration of post pituitary extract Am J Physiol 131 601 605 (Jan) 1941
 - 13 Soderman W A and Engelhardt H T Renal concentration test employing use of pituitary extracts Response of normal subjects Proc Soc Exper Biol & Med 46 633 691 (Apr) 1941
 - 14 Verney E B Absorption and excretion of water Lancet 2 739 744 (Nov) 1946

B Individual Hormones

21 Other Posterior Lobe Principles

- 1 Burn J H The relation of pituitary extract (infundibular lobe) to the fall of blood sugar produced by an ulin J Physiol 57 xxxviii (Feb) 1973
- 2 — The modification of the action of insulin by pituitary extract and other substances J Physiol 57 318 329 (June) 1923
- 3 Corey E L and Britton S W Antagonistic action of desoxycorticosterone and post pituitary extract on chloride and water balance Am J Physiol 133 511 519 (July) 1941
- 4 Neufeld A H and Collip J B Antagonist to adrenalin hyperglycaemia in pituitary extracts Canad M A J 40 537 539 (June) 1939
- 5 — Further studies on antagonist to adrenalin hyperglycaemia in pituitary extracts Endocrinology 25 775 781 (Nov) 1939

C Hypophysectomy

- 1 Allen B M Effects of the extirpation of the anterior lobe of the hypophysis of *Rana pipiens* Biol Bull 32 117 130 1917
- 2 Althausen T L Influence on endocrine organs on intestinal absorption in Essays in Biology Berkeley Univ California Press 1943 pp 11 25
- 3 Artundo A Action dynamique spécifique chez les chiens hypophysectomisés Compt rend Soc de biol 106 139 140 (Jan) 1931
- 4 Aschner H Ueber die Folgeerscheinungen nach Extirpation der Hypophyse Verhandl d deutsch Gesellsch f chir 39 46 49 (Mar) 1910
- 5 — Ueber die Funktion der Hypophyse Pflügers Arch f d ges Physiol 146 1 146 (June) 1912
- 6 Atwell W J Effects of thyrotropic and adrenotropic principles on hypophysectomized amphibia Anat Rec 62 361 379 (July) 1935
- 7 Ball M A Samuels L T and Schott H F Effect of cortical extract on glucose tolerance of adrenalectomized and hypophysectomized rats Proc Soc Exper Biol & Med 35 633 634 (Jan) 1937

- 8 Baumann E J Metzger N and Marne D Total iodine and thyroxine of thyroid after hypophysectomy Endocrinology 31 359 362 (Sept) 1942
- 9 Benedict F G and Hofmans J The metabolism of the hypophysectomized dog J Med Research 25 409 507 (Feb) 1912
- 10 de Bodo H C Bloch H I and Gross I H Role of anterior pituitary in adrenalin hyperglycemia and liver glycogenolysis Am J Physiol 137 124 135 (Aug) 1942
- 11 de Bodo R C Bloch H I and Slater I Role of anterior pituitary in maintenance of normal blood sugar levels and in physiological mobilization of liver glycogen Am J Physiol 137 671 690 (Nov) 1942
- 12 Brauer B Minimum proteico en la insuficiencia hipofisaria Rev Soc argent de biol 7 340 349 1931
- 13 — Le rapport carbone azote dans la vaine minose B des chiens hypophysectomisés Compt rend Soc de biol 108 507 508 (Oct) 1931
- 14 — Echanges azotés et glycémie des chiens hypophysectomisés à jeun Compt rend Soc de biol 107 1195 1198 (July) 1931
- 15 Brauer B and Morea R Métabolisme azoté endogène des rats hypophysectomisés Compt rend Soc de biol 119 881 882 (Apr) 1935
- 16 Carnes W H, Osobold J., and Stoerk H C Parathyroid function in hypophysectomized rat Am J Physiol 139 183 197 (June) 1943
- 1 Chalkoff I L Entenman C Rinehart J F and Reschert F L Development of cirrhosis in liver of dogs deprived of both pituitary and thyroid glands Proc Soc Exper Biol & Med 54 170 171 (Nov) 1943
- 16 Collip J B Anderson E M and Thomson H L The adrenotropic hormone of the anterior pituitary lobe Lancet 2 347 348 (Aug) 1933
- 19 Collip J B Diabetogenic thyrotropic adrenotropic and parathyrotropic factors of the pituitary J.A.M.A 104 827 832 (Mar) 1935
- 20 Cope O The relation of the pituitary to liver glycogen production and utilization J Physiol 88 401 416 (Jan) 1937
- 21 — Endocrine function and amylase activity III Further observations of blood serum amylase activity in relation to pituitary pancreas and thyroid function in the dog and rabbit Endocrinology 25 248 256 (Aug) 1939
- 22 Cope O Kapnick I Lambert A Pratt T D and Verlot M G Endocrine function and amylase activity III Further observations of blood serum amylase activity in relation to pituitary pancreas and thyroid function in the dog and rabbit Endocrinology 25 243 256 (Aug) 1939
- 23 Corkhill A B Marks H F and White W E Relation of the pituitary gland to the action of insulin and adrenalin J Physiol 80 193 205 (Dec) 1934
- 24 Crafts Roger C Effects of hypophysectomy castration and testosterone propionate on hemopoiesis in the adult male rat Endocrinology 29 401 413 (June) 1946
- III Dye J A The glycogenolytic function of the liver in the absence of its assumed humoral and nervous control Am J Physiol 119 299 300 (Apr) 1937
- 26 Entenman C Chalkoff I L and Reichert F L Role of nutrition in response of blood

- ogy pp 507-527 Berkeley Univ California Press 1943
- 105 Russell J A and Bennett L L Carbohydrate storage and maintenance in the hypophysectomized rat *Am J Physiol* 118 196 205 (Jan) 1937
 - 106 Sachs E and MacDonald M E Blood sugar studies in experimental pituitary and hypothalamic lesions *Arch Neurol & Psychiat* 13 335 368 (Mar) 1925
 - 107 Samuels L T and Ball H A Factors in influencing the sugar tolerance curve of hypophysectomized rats *J Pharmacol & Exper Therap* 57 140 141 (Mar) 1936
 - 108 — Carbohydrate metabolism studies in hypophysectomized rats: relation of various methods of glucose administration to blood sugar curve *Endocrinology* 21 380 386 (May) 1937
 - 109 Samuels L T Reinecke R M and Bauman K L Growth and metabolism of young hypophysectomized rats fed by stomach tube *Endocrinology* 33 87 95 (Aug) 1943
 - 110 Sayers G Sayers M A Fry E C White A and Long C N Effect of adrenotropic hormone of anterior pituitary on cholesterol content of adrenals with review of literature of adrenal cholesterol *Yale J Biol & Med* 18 361 392 (Mar) 1944
 - 111 Schaffer N K and Lee M Effect of anterior pituitary growth hormone on protein metabolism *J Biol Chem* 108 355 371 (Feb) 1935
 - 112 Selye H Thymus and adrenals in response of organism to injuries and intoxications *Brit J Exper Path* 17 234 248 (June) 1936
 - 113 — Syndrome produced by diverse noxious agents *Nature* 138 32 (July) 1936
 - 114 — Studies on adaptation *Endocrinology* 21 169 188 (Mar) 1937
 - 115 Selye H and Foglia V G Blood sugar changes in hypophysectomized rats during adaptation to various stimuli *Proc Soc Exper Biol & Med* 39 222 226 (Oct) 1938
 - 116 Shapiro H A and Zwarenstein H Metabolic changes associated with endocrine activity and the reproductive cycle in *Xenopus laevis* I The effects of gonadectomy and hypophysectomy on the calcium content of the serum *J Exper Biol* 10 186 195 (Apr) 1933
 - 117 Shumacker H H Jr and Frier W M The interrelationship of the adrenal cortex and the anterior lobe of the hypophysis *Endocrinology* 18 676 692 (Nov-Dec) 1934
 - 118 Smith P E The effect of hypophysectomy in the early embryo upon the growth and development of the frog *Anat Rec* 11 57 64 (Oct) 1916
 - 119 — Ablation and transplantation of the hypophysis in the rat *Anat Rec* 32 721 (Mar) 1926
 - 120 — The disabilities caused by hypophysectomy and their repair *J.A.M.A.* 88 158 161 (Jan) 1927
 - 121 — Hypophysectomy and a replacement therapy in the rat *Am J Anat* 45 205 273 (Mar) 1930
 - 122 — The effect of hypophysectomy upon the involution of the thymus in the rat *Anat Rec* 47 119 129 (Oct) 1930
 - 123 Soong H Y Assay of insulin content of pancreas in rats receiving anterior pituitary extract *Chine J Physiol* 13 335 341 (June) 1940
 - 124 Taurog A, Chaikoff I L and Bennett L L Influence of hypophysectomy upon plasma iodine and thyroxine content of thyroid gland of rat *Endocrinology* 38 122 126 (Feb) 1946
 - 125 Tyslowitz R Effect of hypophysectomy on concentration of ascorbic acid in adrenals of rat *Endocrinology* 32 103 108 (Jan) 1943
 - 126 Van Dyke H B Physiology and Pharmacology of Pituitary Body Chap 2 p 34 Chicago Univ Chicago Press 1936
 - 127 Vollmer E P Gordon A S Levenstein I and Charipper H A Effects of hypophysectomy upon blood picture of rat *Endocrinology* 25 970 977 (Dec) 1939
 - 128 von Bakay L Jr Über die Beziehungen Zwischen der Hypophyse und den Langerhansschen Inseln *Pflügers Arch f d ges Physiol* 243 733 740 1940
 - 129 White W E Effect of hypophysectomy of rabbit *Proc Roy Soc Brit* 114 64 79 (Nov) 1933
 - 130 White H L Heinbecker P and Rolf D Effects of removal of anterior lobe of hypophysis on some renal functions *Am J Physiol* 136 584 591 (June) 1942
 - 131 — Some endocrine influences on renal function and cardiac output *Am J Physiol* 149 404 417 (May) 1947
 - 132 Williams J R Jr Diaz J T Burch J O and Harrison T R Relation of adrenal glands to action of renal pressor substance *Am J M Sc* 198 212 219 (Aug) 1939
 - 133 Young F G The pituitary gland and carbohydrate metabolism *Endocrinology* 26 345 351 (Feb) 1940
 - 134 Zondek B Ovum Cycle and Menstruation *Essays in Biology* pp 677 687 Berkeley Univ California Press 1943
- ### D Hyperhormonal Effects
- 1 Berg M Experimental studies on production of peptic ulcers by vasomotor alterations (pitressin episodes) *Am J Digest Dis* 7 78 81 (Feb) 1940
 - 2 Bergami G Lesioni gastriche e polmonari consecutive ad alte dosi della frazione vasopressoria dell'ormone retrofossario *Boll Soc Ital Biol Sper* 10 90 93 1935
 - 3 Bischoff F Long M L and Evans R D The posterior pituitary hormone in metabolism II The effect of pitressin and pituitrin upon the carbohydrate reserves of adrenal ectomized rabbits With a histologic report *Am J Physiol* 99 253 260 (Dec) 1931
 - 4 Byrom F H Morbid effects of vasopressin on the organs and vessels of rats *J Path & Bact* 45 1 16 (July) 1937
 - 5 Cooper R and Chamberlain E N The effect of pituitrin on the fatty acid of the liver *J Physiol* 60 69 78 (May) 1925
 - 6 Dodds E C Hills G M Noble R L and Williams P C The posterior lobe of the pituitary gland Its relationship to the stomach and to the blood picture *Lancet* 1 1099 1100 (May) 1935
 - 7 Dodds E C and Noble R L Relation of the posterior lobe of the pituitary gland to anaemia and to blood formation *Nature* 135 788 (May) 1935
 - 8 Dodds E C Noble R L Scarff R W and

- of normal and hypophysectomized dogs *Jap J Med Sci Tr N Pharmacol* 5 56 58 1931
- 67 Koster S Etude expérimentale de la fonction de l'hypophyse chez le chien *Arch internat de physiol* 13 601 603 1928
 - 68 ——— Experimentelle Untersuchungen der Hypophysenfunktion beim Hunde Zweiter (letzter) Teil *Pflügers Arch f d ges Physiol* 224 212 216 1930
 - 69 Koster S and Geerink A Experimentelle Untersuchung der Hypophysenfunktion beim Hunde *Pflügers Arch f d ges Physiol* 222 293 321 (Jan) 1929
 - 70 Lee M O Relation of the anterior pituitary growth hormone to protein metabolism *Proc A Research Nerv & Ment Dis* 17 193 221 1936
 - 71 Lee M and Ayres G H The composition of weight lost and the nitrogen partition of tissues in rats after hypophysectomy *Endocrinology* 20 489 495 (July) 1936
 - 72 Levin L and Leatham J H Relation of pituitary thyroid and adrenal glands to maintenance of normal serum albumin and globulin levels *Am J Physiol* 126 306 313 (Apr) 1942
 - 73 Levine R Hechter O Grossman A and Sokol S Reduced glutathione of tissues and insulin sensitivity *Proc Soc Exper Biol & Med* 40 525 528 (Apr) 1939
 - 74 Long C N H The growth and metabolic hormones of the anterior pituitary *Ann New York Acad Sci* 43 145-4 6 (Feb) 1943
 - 75 Long C N and Lukens F D The effects of adrenalectomy and hypophysectomy upon experimental diabetes in the rat *J Exper Med* 61 465 490 (Apr) 1938
 - 76 Marenzi A D and Gerschlager N L'hypophyse et les substances minérales du sang *Compt rend Soc de biol* 118 488-489 (Nov) 1935
 - 77 Mazzocco P Eléments morphologiques du plasma chez des chiens privés d'hypophyse *Compt rend Soc de biol* 97 594 595 (July) 1927
 - 78 McPhail M R Hypophysectomy of the cat *Proc Roy Soc London A* 117 45 63 (Feb) 1935
 - 79 Meyer O O Stewart G E Thewlis E W and Rusch H P Hypophysis and hematopoiesis *Folia haemat* 37 99 109 (Mar) 1937
 - 80 Miller R A and Riddle O Stimulation of adrenal cortex of pigeons by anterior pituitary hormones and by their secondary products *Proc Soc Exper Biol & Med* 41 518 522 (June) 1939
 - 81 Moon H D Preparation and biological assay of adrenocorticotrophic hormone *Proc Soc Exper Biol & Med* 35 649 652 (Jan) 1937
 - 82 ——— Effect of adrenocorticotrophic hormone on 4-day old rats *Proc Soc Exper Biol & Med* 43 42 44 (Jan) 1940
 - 83 Moore D H Levin L and Leatham J H A—Globulin fraction of serum of normal and hypophysectomized rats *J Biol Chem* 153 349 353 (May) 1944
 - 84 Nelson W O and Gaunt R Initiation of lactation in the hypophysectomized guinea pig *Proc Soc Exper Biol & Med* 34 671 673 (June) 1936
 - 85 Nelson W O Gaunt R and Schweizer M Effects of adrenal cortical compounds on lactation *Endocrinology* 11 325 332 1943
 - 86 Ostler E U and Anderson A H Ketosis in hypophysectomized rat *Biochem J* 33 1094 1098 (July) 1939
 - 87 Ogden E Pace E W and Anderson E Effect of posterior hypophysectomy on renal hypertension *Am J Physiol* 141 389 392 (May) 1944
 - 88 Overbeck G A Reticulocytes in normal and hypophysectomized rats *Arch internat de pharmacodyn et de therap* 54 340-348 (Oct) 1936
 - 89 Overbeck G A and Querido A Hypophysis and blood picture *Arch internat de pharmacodyn et de therap* 60 105 114 (Sept) 1938
 - 90 Perl D Relation of the hypophysis to the spleen I Effect of hypophysectomy on growth and regeneration of spleen tissue II The presence of a spleen stimulating factor in extracts of anterior hypophysis *J Exper Med* 63 599 615 (Apr) 1936
 - 91 ——— The Pituitary Gland pp 471-495 Baltimore Williams & Wilkins 1938
 - 92 Perl D and Sandberg M The effect of complete and partial hypophysectomy in adult albino rats on nitrogen calcium and phosphorus metabolism *Endocrinology* 20 481 488 (Apr) 1936
 - 93 Phillips R A and Robb F Carbohydrate metabolism studies in hypophysectomized albino rats *Am J Physiol* 109 82 83 (July) 1934
 - 94 ——— Metabolism studies in albino rat carbohydrate studies after hypophysectomy *Endocrinology* 25 187 191 (Aug) 1939
 - 95 Pickford W and Ritchie A E Experiments on hypothalamic pituitary control of water excretion in dogs *J Physiol* 104 105 128 (Oct.) 1945
 - 96 Purley L I and Anderson E M The effect of the growth and thyrotrophic hormones of the anterior pituitary upon the calcium metabolism of the rat *Am J Physiol* 109 85 (July) 1934
 - 97 Querido A and Overbeck G A Hypophysis and bloodpicture *Arch internat de pharmacodyn et de therap* 61 475 490 (Apr) 1939
 - 98 Reese J D and Bloom H D The Golgi apparatus of the cells of the adrenal cortex after hypophysectomy and on the administration of adrenocorticotrophic hormone *Anat Rec* 70 543 556 (Apr) 1938
 - 99 Remhardt W O Studies on Growth of Lymph Nodes Thymus and Spleen in Rat Essays in Biology pp 437-497 Berkeley Univ California Press 1943
 - 100 Richier C F and Wislocki G B Anatomical and behavior changes produced in the rat by complete and partial extirpation of the pituitary gland *Am J Physiol* 95 431-492 (Nov) 1930
 - 101 Rusch H J A The relation of the anterior pituitary to carbohydrate metabolism *Physiol Rev* 18 1 27 (Jan) 1938
 - 102 ——— Relationship of anterior pituitary and adrenal cortex in metabolism of carbohydrate *Am J Physiol* 128 552 561 (Feb) 1940
 - 103 ——— Anterior pituitary in carbohydrate metabolism of emaciated rat *Am J Physiol* 126 95 104 (Mar) 1942
 - 104 ——— Relationship of Anterior Pituitary to Thyroid and Adrenal Cortex in Control of Carbohydrate Metabolism *Essays in Biol*

- disoni Virchow's Arch f path Anat 247 421 447 (June) 1923
- 18 — Zur Pathologie des Morbus Addisoni (Be funde in Hypophyse und Nebennieren) Beitr z path Anat u z allg Path 78 283 296 (Sept.) 1927
 - 19 Lehmann J Die Struktur des Hirnanhangs nebennierenloser Ratten Ztschr f d ges exper Med 53 129 140 1929
 - 20 — Zur Frage der Geschlechtsspezifität der Keimdrüseninkrete Inkretwirkung und Veränderung der Kastrationshypophyse der Ratte Pfleger's Arch f d ges Physiol 216 729 748 1927
 - 21 Meites J and Turner C W Effect of sex hormones on pituitary lactogen and crop glands of common pigeons Proc Soc Exper Biol & Med 64 465 468 (Apr) 1947
 - 22 — Effect of thiouracil and estrogen on lactogenic hormone and weight of pituitaries of rats Proc Soc Exper Biol & Med 64 488 492 (Apr) 1947
 - 23 Müller R Eitel H and Loeser A Der thyreoepotrope Wirkstoffgehalt der menschlichen Hypophyse Arch f exper Path u Pharmacol 179 427 439 1935
 - 24 Payne F Cytology of anterior pituitary of fowl Biol Bull 82 79 111 (Feb) 1942
 - 25 Philipp M Über den Zusammenhang von Histologie und innersekretorischer Wirkung des Hypophysenvorderlappens Zentralbl f Gynak 54 3076 3096 (Dec) 1930
 - 26 Purves H D and Griesbach W E Observations on the acidophil cell changes in the pituitary in thyrotoxic deficiency states I Acidophil degeneration in relation to goitrogenic agents and extrathyroidal thyroxine synthesis Brit J Exper Path 27 170 179 (June) 1946
 - 27 Rasmussen A T The percentage of the different types of cells in the anterior lobe of the hypophysis in the adult human female Am J Path 9 459 471 (July) 1933
 - 28 — Pituitary Gland 118 Baltimore Williams & Wilkins 1938
 - 29 Reese J D Koneff A A and Wainman P Cytological differences between castration and thyroidectomy basophils in the rat hypophysis in Essays in Biology pp 473 482 Berkeley Univ California Press 1943
 - 30 Rjoch D McK Paths of secretion from the hypophysis is A Research Nerv. & Ment Dis Proc 17 151 171 1938
 - 31 Saxton J and Loeb L Thyroid stimulating and gonadotropic hormones of the human anterior pituitary gland at different ages and in pregnant and lactating women Anat Rec 69 61 279 (Aug) 1937
 - 32 Schleidt J Ueber die Hypophyse bei feminierten Männchen und maskulierten Weibchen Zentralbl f Physiol 27 1170 1172 1914
 - 33 Schooley J P and Riddle O Morphological basis of pituitary function in pigeons Am J Anat 62 313 349 (Mar) 1938
 - 34 Severinghaus A E The cytology of the pituitary gland in The Pituitary Gland pp 69 117 Baltimore Williams & Wilkins 1938
 - 35 — Cytology of pituitary gland A Research Nerv & Ment Dis Proc 17 69 117 1938
 - 36 — Cellular changes in the anterior hypophysis with special reference to its secretory activities Physiol Rev 17 556 588 (Oct) 1937
 - 37 Shumacker H W, and Firor W M The interrelationship of the adrenal cortex and the anterior lobe of the hypophysis Endocrinology 18 676 692 (Nov Dec) 1934
 - 38 Smelser H K Differential concentration of hormones in central and peripheral zones of bovine anterior pituitary gland Endocrinology 34 39-43 (Jan) 1944
 - 39 Smith P E and MacDowell E C An hereditary anterior pituitary deficiency in the mouse Anat Rec 46 249 257 (Aug) 1930
 - 40 — Differential effect of hereditary mouse dwarfism on anterior pituitary hormones, Anat Rec 50 93 (July) 1931
 - 41 Spark C Structure of human anterior pituitary gland after administration of estrogenic hormones J Clin Endocrinol 3 367 374 (June) 1943
 - 42 Susman W The significance of the different types of cells of the anterior pituitary Endocrinology 19 592 595 (Sept Oct) 1935
 - 43 Terplan K and Sanes S Pathological report of case of Addison's disease treated with cortin Endocrinology 16 69 76 (Jan Feb) 1932
 - 44 Van Dyke H H Physiology and Pharmacology of the Pituitary Body Vol 2 pp 10 31 Univ Chicago Press 1939
 - 45 Witschi E and Riley M Quantitative studies on the hormones of human pituitaries Endocrinology 26 565 576 (Apr) 1940
 - 46 Zondek B and Krohn H Hormone des Zwischenlappens der Hypophyse (Intermedia) II Intermedia im Organismus (Hypophyse Gehirn) Klin Wchnschr 11 849 853 (May) 1932

VII CHEMISTRY

- 1 Bonsnes R W and White A Fractionation of saline extracts of anterior pituitary tissue Endocrinology 26 990 998 (June) 1940
- 2 Cieres L S and White A Isolation of purified protein with marked thyrotropic activity from beef pituitary tissue Federation Proc 1 105 (Mar) 1942
- 3 Collip J H Pituitary gland in relation to metabolism West J Surg 47 1 3 (Jan) 1949
- 4 Crandall L A Jr and Cherry I S Effects of insulin and glycine on hepatic glucose output in normal hypophysectomized adrenal demineralized and adrenalectomized dogs Am J Physiol 125 658 673 (Apr) 1936
- 5 Evans H M Meyer K and Simpson M H Growth and Gonad Stimulating Hormones of Anterior Hypophysis 67 Berkeley, Univ California Press 1943
- 6 Fevold H L Hisaw F L and Leonard S L The gonad stimulating and the luteinizing hormones of the anterior lobe of the hypophysis Am J Physiol 97 291 301 (May) 1931
- 7 Greep R O Van Dyke H B and Chow H F Separation in nearly pure form of luteinizing (interstitial cell stimulating) and follicle stimulating (gametogenic) hormones of the pituitary gland J Biol Chem 133 289 290 (Feb) 1940
- 8 — Gonadotropins of swine pituitary various biological effects of purified thyliactrin (FSH) and pure metakentrin (ICSH) Endocrinology 30 635 649 (May) 1944
- 9 Irving G W Chemistry and Physiology of Hormones pp 28-46 Washington Am Assoc Advancement Sc 1944

- Williams P C Pituitary control of alimentary blood flow and secretion. Changes in the stomach produced by the administration of posterior pituitary extract. *Proc. Roy Soc London* 8 B 123 2 26 (June) 1937
- 9 Dodds E C, Noble R L and Smith E R A gastric lesion produced by an extract of the pituitary gland. *Lancet* 2 918 919 (May) 1934
- 10 Engel R, McQuarrie I and Zueglar M Untersuchungen über den Mineralgehalt nach Zufuhr von Hypophysenhinterlappensubstanz. *Arch f exper Path u Pharmacol* 173 249 259 1933
- 11 Gilman A and Goodman L Pituitary anemia. *Am J Physiol* 118 241 250 (Feb) 1937
- 12 Himwich H F and Paulus J Effects of posterior pituitary extracts on the lactic acid of the blood. *Proc Soc Exper Biol & Med* 28 331-332 (Dec) 1930
- 13 Holtz P and Jancke G Die Wirkung der Hormone des Hypophysenhinterlappens auf den intraokulären Druck. *Arch f exper Path u Pharmacol* 181 494 507 1936
- 14 Houssay B A and di Benedetto E Action hyperglycémisante de l'extract rétropituitaire (Abstract). *Compt rend Soc de biol* 114 793 95 1933
- 15 Li C H and Evans H M The biochemistry of pituitary growth hormone. Recent Progress in Hormone Research, edited by Gregory Pincus Vol 3 pp 1-44 New York Acad Press 1948
- 16 McFarlane W H and McPhail M K Pituitary injections and the blood picture in the normal and hypophysectomized guinea pig. *Am J M Sc* 193 385 389 (Mar) 1937
- 17 McIntire A R and Sievers R F Some effects of posterior lobe pituitary extract upon the serum and urine of normal dogs. *J Pharmacol & Exper Therap* 49 229 236 (Oct) 1933
- 18 Nedetz A J Pressor reaction and gastric ulcer. *Proc Soc Exper Biol & Med* 34 150-151 (Mar) 1936
- 19 Nitescu I I and Benetato G Action des substances rétropituitaires hypertensive et ocytoclique sur les graisses du sang. *Compt rend Soc de biol* 105 110 (Oct) 1930
- 20 Page I H Vascular action of fresh urine and extracts thereof. *Proc Soc Exper Biol & Med* 32 30 304 (Nov) 1934
- 21 Raab W Blutfett und Blutfettreaktionen bei Fettsucht (Hypothymusresection). *Ztschr f d ges exper Med* 94 284 292 1934
- 22 Selye H, Stehle R L and Collip J B Recent advances in the experimental production of gastric ulcers. *Canad M A J* 34 339 (Mar) 1936
- 23 Simpson M E, Evans H M and Li C H Injurious action of pituitrin on rat testis. *Proc Soc Exper Biol & Med* 51 318 320 (Dec) 1942
- 24 Urech C I, Groze I and Retezescu Action de l'extract du lobe postérieur de l'hypophyse (pitocine et pituitrine) sur le calcium et le phosphore du sang. *Compt rend Soc de biol* 103 1363 1364 (May) 1930
- 25 Van Dyke H B The Physiology and Pharmacology of the Pituitary Body. pp 336 365 Chicago Univ Chicago Press 1936
- 26 Voegtlin C, Thompson J W and Dunn E R Pituitrin hyperglycaemia and the antagonism between pituitrin and insulin. *J Pharmacol & Exper Therap* 25 137 (Mar) 1915
- 27 Watrin J and Francois R Hypertrophie expérimentale du cœur de cobaye par injections répétées de posthypophyse. *Compt rend Soc de biol* 125 357 358 (Jul) 1937

E Histophysiology

- 1 Addison W H The cell changes in the hypophysis of the albino rat after castration. *J Comp Neurol* 28 441-461 1917
- 2 Baker B L and Everett N B Effect of small doses of diethylstilbestrol on anterior hypophysis of immature rat. *Endocrinology* 34 254 264 (Apr) 1944
- 3 Bugarl J H Hypophysis of human castrate. *Bull Johns Hopkins Hosp* 34 157 164 (Mar) 1934
- 4 ——— Some observations on basophil cells of human hypophysis. *Tr Edinburgh Obst Soc* 4 113 124 1935
- 5 Crooke A C and Russell D S The pituitary gland in Addison's disease. *J Path & Bact* 40 225 283 (Mar) 1935
- 6 Dobyns B M Studies on exophthalmos produced by thyrotropic hormone. Study of exophthalmos produced by various thyrotropic hormones and influence of testes on exophthalmos. *Surg Gynec & Obst* 82 290 300 (Mar) 1946
- 7 Ehrhardt K Klinische und tierexperimentelle Untersuchungen über das Melanophorenagens des Hypophysenhinterlappens. *Arch f Gynak* 148 265 270 1932
- 8 Fichera G Sur l'hypertrophie de la glande pituitaire consécutive à la castration. *Arch ital de biol* 43 405-426 1905
- 9 Friedgood H B and Dawson A B Cytologic evidence of gonadotropic activity of rabbit's anterior hypophysis. *Endocrinology* 22 674 686 (June) 1938
- 10 ——— Physiological significance and morphology of carmine cell in cats anterior pituitary. *Endocrinology* 26 1072 1081 (June) 1940
- 11 ——— Inhibition of carmine cell reaction in pituitaries of cats which mate but do not ovulate. *Endocrinology* 30 252 257 (Feb) 1942
- 12 Friedgood H B and Pincus G Studies on conditions of activity in endocrine organs. XXX. The nervous control of the anterior hypophysis as indicated by maturation of ova and ovulation after stimulation of cervical sympathetic. *Endocrinology* 19 710-718 (Nov Dec) 1935
- 13 Griesbach W M Studies on experimental goitre. II Changes in the anterior pituitary of the rat produced by brassica seed diet. *Brit J Exper Path* 22 245 249 (Oct) 1941
- 14 Harrop G A and Weinstein A Addison's disease treated with uprational cortical hormone (Swingle-Pfaffner). *JAMA* 98 1525 1531 (Apr) 1932
- 15 Heller H Multiplicity of pituitary hormones. *Nature* 147 178 (Feb) 1941
- 16 Henderson W R and Rowlands I W Gonadotropic activity of anterior pituitary gland in relation to increased intracranial pressure. *Brit M J* 1 1094 1097 (May) 1938
- 17 Kraus E J Zur Pathologie der basophilen Zellen der Hypophyse. Zugleich ein Beitrag zur Pathologie des Morbus Basedowi und Ad

- Hormone pp 47 57 Washington D C Am Assoc Advancement Sc 1944
- 13 Marx W Simpson M E and Evans H M Bioassay of growth hormone of anterior pituitary *Endocrinology* 30 1 10 (Jan) 1942
 - 14 — Specificity of epiphyseal cartilage test for pituitary growth hormone *Proc Soc Exper Biol & Med* 55 250 252 (Apr) 1944
- ### C Gonadotropins
- 1 Fevold H L Extraction and standardization of pituitary follicle stimulating and luteinizing hormones, *Endocrinology* 24 435 446 (Apr) 1939
 - 2 Greep R O Van Dyle H B and Chow B F The effect of pituitary gonadotropins on the testicles of hypophysectomized immature rats *Anat Rec* 78 88 Suppl (Dec) 1940
 - 3 — Use of anterior lobe of prostate gland in assay of metakentrin *Proc Soc Exper Biol & Med* 46 644 649 (Apr) 1941
 - 4 — Gonadotropins of the same pituitary I Various biological effects of purified thyliakentrin (FSH) and pure metakentrin (ICSH), *Endocrinology* 30 635 649 (May) 1942
 - 5 Evans H M Korpi K Simpson M E Pencharz R I and Wonder D H On the separation of the interstitial cell stimulating luteinizing and follicle stimulating fractions in the anterior pituitary gonadotropic complex *Univ California Publ Anat* 2 255 274 1936
 - 6 Jensen H Simpson M E Tolksdorf S and Evans H M Chemical fractionation of gonadotropic factors present in sheep pituitary *Endocrinology* 25 57 62 (July) 1939
 - 7 Jensen H and Tolksdorf S Relation of anterior pituitary to sex and metabolism *Endocrinology* 25 429 436 (Sept.) 1939
 - 8 Levin L and Tyndale H H The quantitative assay of follicle stimulating substances *Endocrinology* 21 619 628 (Sept.) 1937
 - 9 La C H Simpson M E and Evans H M Purification of pituitary interstitial cell stimulating hormone *Science* 92 355 356 (Oct) 1940
 - 10 — Comparison of methods for standardization of pituitary interstitial cell stimulating hormone (ICSH) *Endocrinology* 30 977 984 (June) 1942
 - 11 Witschi E Quantitative determination of follicle stimulating and luteinizing hormones in mammalian pituitaries and discussion of gonadotropic quotient *Endocrinology* 27 437 446 (Sept) 1940
- ### D Thyrotropic Hormone
- 1 Aron M Action de la préhypophyse sur la thyroïde chez le cobaye *Compt rend Soc de biol* 102 682 684 (Nov) 1929
 - 2 — Particularités histologiques de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse *Compt rend Soc de biol* 103 145 147 (Jan) 1930
 - 3 — Note de technique sur la mise en évidence et l'évaluation quantitative des faibles taux de thyroïde stimuline préhypophysaire présents dans le sang ou l'urine *Compt rend Soc de biol* 109 218 220 (Jan) 1932
 - 4 — Sur le titrage biologique de la thyroïde stimuline préhypophysaire le seul des matériaux dans la thyroïde des cobayes traités *Compt rend Soc de biol* 123 250-253 (Ju'j) 1936
 - 5 Aron M and Klein M Sur la présence dans l'urine humaine d'une substance douée de la même action sur la thyroïde que l'extrait préhypophysaire et sur l'interprétation de la réaction de diagnostic de la grossesse *Compt rend. Soc de biol* 103 707 704 (Feb) 1930
 - 6 Bergman A J and Turner C W Comparison of guinea pig and chick thyroid in assay of the thyrotropic hormone *Endocrinology* 24 656 664 (May) 1939
 - 7 Ciereszko L S Preparation of pituitary thyrotropic hormone *J Biol Chem* 160 585 592 (Oct) 1945
 - 8 Collip J H The standardization of anterior pituitary hormones *Am J Obst & Gynec* 33 1010 1016 (June) 1937
 - 9 Cope C L Young chick as test for thyrotropic hormone *J Physiol* 94 353 364 (Dec.) 1938
 - 10 Cuyler W K Stimmel H F and McCullagh D R Quantitative studies with the thyrotropic hormone *J Pharmacol & Exper Therap* 58 286 293 (Nov) 1936
 - 11 Dvoskin E Intracellular colloid droplets as basis for thyrotropic hormone assay in chick *Endocrinology* 41 220 229 (Sept.) 1947
 - 12 Hertz S and Oastler E G Assay of blood and urine for thyrotropic hormone in thyrotoxicosis and myxedema *Endocrinology* 20 520 525 (July) 1936
 - 13 Heyl J G and Laqueur E Zur quantitativen Bestimmung der thyreotropen Wirkung von Hypophysenvorderlappen Präparaten und die Einheit des thyreotropen Hormons *Arch in internat de pharmacodyn et de therap* 49 338 354 (Jan) 1935
 - 14 Junkmann K and Loeser A Die Wertbestimmung des thyreotropen Hormons der Hypophyse *Arch f exper Path u Pharmacol* 188 474 488 1938
 - 15 Junkmann, K. and Schneller W Über das thyreotrope Hormon des Hypophysenvorderlappens *Klin Wchnschr* 11 1176-1177 (July) 1932
 - 16 Kuppen A A and Loeb L The relation between the quantity of thyroid stimulating hormone of the anterior pituitary gland administered and the proliferative activity and hypertrophy of the thyroid acini in guinea pig *J Pharmacol* 54 46 257 1935
 - 17 Loeser A Die Darstellung, thyreotrop wirkender Extrakte aus Hypophysenvorderlappen *Arch f exper Path u Pharmacol* 166 693 702 1932
 - 18 McCullagh D R and Stimmel B F Biochemical method for assay of thyrotropic hormone of pituitary gland *J Biol Chem* 109 149 150 (May) 1935
 - 19 Rawson R W and Starr P Direct measurement of weight of thyroid epithelium: method of assay of thyrotropic substance clinical application *Arch Int Med* 61 726 738 (May) 1938
 - 20 Rowlands I W and Parkes A S Quantitative study of the thyrotropic activity of anterior pituitary extracts *Biochem J* 28 1829 1843 1934
 - 21 Third Internat Conf on the Stand of Hormones *Bull Health Organ League of Nations* 7 1938

- 10 Jorgensen M N and Wade N J Preparation of thyrotropic hormone *Endocrinology* 28 405-411 (Mar) 1941
 - 11 Li C H Studies on pituitary lactogenic hormone diffusion and viscosity measurements *J Biol Chem* 146 633 638 (Dec) 1942
 - 12 Li C H and Evans H M Isolation of pituitary growth hormone *Science* 80 183 184 (Mar) 1944
 - 13 — The biochemistry of pituitary growth hormone Recent progress in hormone research Vol 3 pp 3-44 New York Acad Press 1943
 - 14 — The Hormones: Physiology Chemistry and Applications Edited by Gregory Pincus and Kenneth A Thimann Vol 1 pp 644 648 New York Acad Press 1943
 - 15 Li C H Evans H M and Simpson M E Adrenocorticotrophic hormone *J Biol Chem* 149 413-424 (Aug) 1943
 - 16 — Isolation and properties of anterior hypophyseal growth hormone *J Biol Chem* 159 353 366 (July) 1945
 - 17 Li C H Simpson M E and Evans H M Purification of pituitary interstitial cell stimulating hormone *Science* 92 355 356 (Oct) 1940
 - 18 — Interstitial cell stimulating hormone method of preparation and some physico-chemical studies *Endocrinology* 27 803 808 (Nov) 1940
 - 19 Li C H Lyons W R, and Evans H M Studies on pituitary lactogenic hormone molecular weight of pure hormone *J Biol Chem* 140 43 53 (July) 1941
 - 20 Li C H Simpson M E and Evans H M Physico-chemical characteristics of interstitial cell stimulating hormone from sheep pituitary glands *J Am Chem Soc* 64 367 369 (Feb) 1942
 - 21 — Isolation of adrenocorticotrophic hormone from sheep pituitaries *Science* 96 450 (Nov) 1942
 - 22 — Effect of various reagents on adrenocorticotrophic hormone *Arch Biochem* 9 259 264 (Mar) 1946
 - 23 Marx W Simpson M E and Evans H M Purification of growth hormone of anterior pituitary *J Biol Chem* 147 77 89 (Jan) 1943
 - 24 Reiss M and Golla Y M L Purification of anterior pituitary corticotrophic hormone *Nature* 155 456 (Apr) 1945
 - 25 Sayers G White A and Long C N Preparation of pituitary adrenotropic hormone *Proc Soc Exper Biol & Med* 52 199 200 (Mar) 1943
 - 26 — Preparation and properties of pituitary adrenotropic hormone *J Biol Chem* 149 425 436 (Aug) 1943
 - 27 Shedlovsky T Rothen A Greep H O Van Dyke H H and Chow H F Isolation in pure form of interstitial cell stimulating (luteinizing) hormone of anterior lobe of pituitary gland *Science* 92 178 180 (Aug) 1940
 - 28 Stehle M L and Fraser A M The purification of the pressor and oxytocic hormones of the pituitary gland and some observations on the chemistry of the products *J Pharm* 55 136 151 (Oct) 1935
 - 29 Stehle R L and Truster S M Additional data concerning chemistry of pressor and oxytocic hormones of pituitary gland *J Pharmacol & Exper Therap* 63 343 352 (Apr) 1939
 - 30 Van Dyke H H Chow H F Greep R O and Rothen A Isolation of protein from pars neuralis of ov pituitary with constant oxytocic pre- or and diuresis inhibiting activities *J Pharmacol & Exper Therap* 74 190 209 (Feb) 1942
 - 31 White A The Chemistry and Physiology of Hormones pp 1 25 Washington H E Am Assoc Advancement Sc 1944
 - 32 — Preparation and chemistry of anterior pituitary hormones (Summary), *Physiol Rev* 26 574 608 (Oct) 1946
 - 33 White A Catchpole H R and Long C N A crystalline protein with high lactogenic activity *Science* 86 82 83 (July) 1937
 - 34 White A, Bonnes H W and Long C N Prolactin *J Biol Chem* 143 447 464 (Apr) 1942
 - 35 White A and Ciereszko L Purification of the thyrotropic hormone of the anterior pituitary *J Biol Chem* 140 cxxxix cxi (July) 1941
- VIII BIO ASSAY**
- B Growth Hormone**
- 1 Chou C, Chang C, Chen G and Van Dyke H B Observations on the quantitative assay of growth promoting extract of the hypophysis, *Endocrinology* 22 322 334 (Mar) 1938
 - 2 Evans H M Glandular Physiology and Therapy p 19 Chicago A M A 1942
 - 3 Evans H M, and Simpson M E Hormones of anterior hypophysis *Am J Physiol* 98 511 546 (Oct) 1931
 - 4 Evans H M, Simpson M E Marx W, and Kibrick E Bioassay of pituitary growth hormone Width of proximal epiphyseal cartilage of tibia in hypophysectomized rats *Endocrinology* 32 13 16 (Jan) 1943
 - 5 Evans H M Uyei N Bartz Q R and Simpson M E The purification of the anterior pituitary growth hormone by fractionation with ammonium sulfate *Endocrinology* 22 483 492 (Apr) 1937
 - 6 Freud J, and Dingemans E Seven years experience of the action of a growth hormone preparation on rats *Acta Brevia Neerland* 14 89 93 1946
 - 7 Freud J, and Levie L H Hypophyse und Schwanzwachstum der Ratte Ein Test für Wachstumshormon *Arch internat de pharmacodyn et de therap* 59 232 242 (June) 1938
 - 8 Freud J Levie L H and Kroon D B Observations on growth (chondrotrophic) hormone and localization of its point of attack *J Endocrinol* 1 56 64 (June) 1939
 - 9 Greenspan F H Li C H Simpson M E and Evans H M Bioassay of hypophyseal growth hormone the tibia test *Endocrinology* 45 455-463 (Nov) 1949
 - 10 Goss H and Gregory P W Glutathione concentration of livers and muscles of rats following injection of hypophyseal growth hormone *Proc Soc Exper Biol & Med* 32 681 683 (Feb) 1935
 - 11 Lee M Pituitary Gland pp 193 217 Baltimore Williams & Wilkins 1938
 - 12 Marx W and Evans H M Chemistry and Physiology of Hormones Pituitary Growth

- 2 Houchin O M and Turner C W Relation of pituitary to blood lipids *Endocrinology* 24 638 644 (May) 1939
 - 3 — A method of assay for the fat metabolism hormone of the anterior pituitary *Endocrinology* 23 216 220 (Aug) 1939
- J Specific Metabolic Principle**
- 1 Billingslev, L W O'Donovan D K and Collip J B The specific metabolic principle of the pituitary *Endocrinology* 24 63 68 (Jan) 1939
 - 2 O'Donovan D K and Collip J B The specific metabolic principle of the pituitary and its relation to the melanophore hormone *Endocrinology* 23 718 746 (Dec) 1938
- K Melanophore Stimulating Factor**
- 1 Abramowitz A A The role of the hypophyseal melanophore hormone in the chromatic physiology of *Fundulus* *Biol Bull* 73 134 142 1937
 - 2 — New method for biological assay of intermedin *J Pharmacol & Exper Therap* 69 156 164 (June) 1940
 - 3 Bottger G Über das pigmenthormon I Mitteilung Der Test *Ztschr f d ges exper Med* 101 42-47 1937
 - 4 — Über das pigmenthormon II Mitteilung Zur Darstellung und zur Frage der Diuresiswirkung *Ztschr f d ges exper Med* 101 48 54 1937
 - 5 — Über das pigmenthormon III Mitteilung Zur Frage der Einheitlichkeit und über die aktive Substanz alkalischer Extrakte *Ztschr f d ges exper Med* 101 55 61, 1937
 - 6 Calloway N O McCormack R W and Singh N P Studies on chemistry of melanophore hormone of pituitary gland critical evaluation of assay methods *Endocrinology* 30 423 429 (Mar) 1942
 - 7 Fenn W O Active principles of the pituitary posterior lobe *J Physiol* 59 xxxv xxxvi (Oct) 1925
 - 8 Hogben L T and Slome D The pigmentary effector system VI The dual character of endocrine co-ordination in amphibian colour change *Proc Roy Soc London* 108 10 53 1931
 - 9 Jores A Untersuchungen über das Melanophorenhormon und einen Nachweis im menschlichen Blut *Ztschr f d ges exper Med* 87 265 282 1933
 - 10 Kleinholz L H and Rahn H Distribution of intermedin new biological method of assay and results of tests under normal and experimental conditions *Anat Rec* 76 157 172 (Feb) 1940
 - 11 Landgrebe F W and Waring H Biological assay and standardization of melanophore expanding pituitary hormone *Quart J Exper Physiol* 33 1 III (Jan) 1944
 - 12 Oldham F K Pharmacology and anatomy of hypophysis of armadillo *Anat Rec* 72 265 291 (Nov) 1938
 - 13 Teague E S Biological assay of melanophore hormone of pituitary gland *Endocrinology* 25 962 964 (Dec) 1939
 - 14 Zondek B, and Krohn H Hormon des Zwischenlappens der Hypophyse (Intermedin) II Intermedin im Organismus (Hypophyse Gehirn) *Klin Wchrschr* 11 849 853 (May) 1932
- L Vasopressin**
- 1 Hamilton H C The pharmacological assay of pituitary preparations *J Am Pharm A* 1 1117 1119 1912
 - 2 Hamilton H C and Powe L W Pituitary standardization *J Lab & Clin Med* 2 120 129 (Nov) 1916
 - 3 Hogben L T, Schlapp W and Macdonald A D Studies on the pituitary IV Quantitative comparison of pressor activity *Quart J Exper Physiol* 14 301 318 1924
 - 4 Kamm O Aldrich T H Grote I W, Rowe L W and Bugbee E P The active principles of the posterior lobe of the pituitary gland I The demonstration of the presence of two active principles II The separation of the two principles and their concentration in the form of potent solid preparations *J Am Chem Soc* 50 573 601 (Feb) 1928
 - 5 Rowe L W Studies on oxytocin and vasopressin pressor action *Endocrinology* 13 203 212 (Mar-Apr) 1929
 - 6 Simon A The secretion of the posterior lobe of the hypophysis after the administration of drugs *J Pharmacol & Exper Therap* 49 375 386 (Nov) 1933
 - 7 Swanson E E A study of the pressor method for the standardization of pituitary extract *J Lab & Clin Med* 14 754 763 (May) 1929
- M Oxytocin**
- 1 Burn J H and Dale H H On the physiological standardization of extracts of the posterior lobe of the pituitary body *Med Res Council Spec Rep* No 69 1922
 - 2 Coon J M New method for assay of posterior pituitary extracts *Arch internat de pharm et de therap* 62 79 99 (May) 1919
 - 3 Dale H H and Laidlaw P P A method of standardizing pituitary (infundibular) extracts, *J Pharmacol & Exper Therap* 4 75 95 (Sept) 1912
 - 4 Heller H Effect of hydrogen ion concentration on stability of antidiuretic and vasopressor activities of posterior pituitary extract *J Physiol* 96 337 347 (Aug) 1939
 - 5 Morrell C A Allmark M G and Bachinski W M On biological assay of oxytocic activity of pituitary extract (posterior lobe) *J Pharmacol & Exper Therap* 70 440-449 (Dec) 1940
 - 6 Péneau H Prudhomme M and Simonnet H Utilisation de l'utérus de certains ruminants pour le dosage du pouvoir oxytocique des extraits post hypophysaires *J de pharm et chim* 14 163 168 1931
 - 7 Schubel K Über die kombinierte Wirkung von Chinin und Myopophysin auf den Uterus der lebenden Katze *Arch f exper Path u Pharmacol* 138 146 147 1928
 - 8 Sealock R H and du Vigneaud V Studies on the reduction of pitressin and pitocin with cysteine *J Pharmacol & Exper Therap* 54 433-447 (Aug) 1935

- 22 Smelser H K Assay of thyrotropic hormone on one day old chicks *Proc Soc Exper Biol & Med* 37 383 390 (Nov) 1937
- 23 — Chick thyroid responses as basis for thyrotropic hormone assay *Endocrinology* 23 429 435 (Oct) 1938
- 24 Spaul H A Experiments on the injection of pituitary body (anterior lobe) extracts to axolotls, *Brit J Exper Biol* 2 33 55 (Oct) 1924
- 25 Starr P. and Rawson R W Graphic representation of thyroid response to stimulation by thyrotropic hormone *Proc Soc Exper Biol & Med* 35 603 605 (Jan) 1937
- 26 Starr P., Rawson R W., Smalley R. E., Doty E. and Patton H Microhistometric method applied to thyrotropic hormone assay *West J Surg* 47 6 75 (Feb) 1939
- 27 Stimmel B F., McCullagh D R and Picha V The thyrotropic hormone of the pituitary gland and iodine metabolism *J Pharmacol & Exper Therap* 57 49 55 (May) 1936
- 28 Wicke J Einfluss der Fixierung auf das histologische Bild der Schilddrüse bei Meerschweinchen *Acta brev Neerland* 5 99 1935

E Adrenocorticotrophic Hormone

- 1 Aitwood E B and Tyslowitz R An assay method for corticotrophin, *Federation Proc.* 1 4 (Apr) 1942
- 2 Bates, R. W., Riddle O and Miller R A Preparation of adrenotropic extracts and their assay on 2-day chicks *Endocrinology* 27 781 792 (Nov) 1940
- 3 Blumenthal H T Adrenal cortex stimulating substance in female human urine *J Lab & Clin Med* 30 428-432 (May) 1945
- 4 Collip J B William Henry Welch Lectures Some recent advances in physiology of anterior pituitary *J Mt Sinai Hosp* 1 28 71 (May June) 1934
- 5 Collip J B Anderson E M and Thomson M L The anterior pituitary lobe. Fractionation of active principles *Lancet* 1 1203 1 09 (May) 1933
- 6 Li C H., Simpson M E and Evans H M Isolation of adrenocorticotrophic hormone from sheep pituitaries *Science* 96 450 (Nov) 1942
- 7 Moon H D Preparation and biological assay of adrenocorticotrophic hormone *Proc Soc Exper Biol & Med* 35 649 652 (Jan) 1937
- 8 — Effect of adrenocorticotrophic hormone in 4-day-old rats *Proc Soc Exper Biol & Med* 43 42-44 (Jan) 1940
- 9 Reiss M Bähnt J Oestreicher F., and Aronson V Zur morphogenetischen Wirkung und biologischen Eichung des corticotropen Wirkstoffes *Endokrinologie III* 1 10 1936
- 10 Sayers G Sayers M A Liang T Y and Long C N Effect of pituitary adrenotropic hormone on cholesterol and ascorbic acid content of adrenal of rat and guinea pig *Endocrinology* 38 1 9 (Jan) 1946
- 11 Sayers M A Sayers G and Woodbury L A The assay of adrenocorticotrophic hormone by the adrenal ascorbic acid-depletion method *Endocrinology* 42 379 393 (May) 1948
- 12 Sayers G White A and Long C N Preparation and properties of pituitary adrenotropic hormone *J Biol Chem* 149 425 436 (Aug) 1943
- 13 Simpson M E Evans H M and Li C H

Bioassay of adrenocorticotrophic hormone *Endocrinology* 33 261 268 (Nov) 1943

F Lactogenic Hormone

- 1 Bates E W Methods for Assay of Prolactin Cold Spring Harbor Symposia on Quantitative Biology New York Biological Laboratory Vol 5 p 191 1937
- 2 Bergman A J., Meites J and Turner C W Comparison of methods of assay of lactogenic hormone *Endocrinology* 26 716 722 (Apr) 1940
- 3 Gardner W U. and Turner C W The Function Assay and Preparation of Galactin a Lactation Stimulating Hormone of the Anterior Pituitary and an Investigation of the Factors Responsible for the Control of Normal Lactation *Columbia Univ Missouri Agr Exp Sta Res Bull* 196 1933
- 4 Hall S R Study of crop-sac weight method for prolactin assay *Endocrinology* 34 1 13 (Jan) 1944
- 5 Lyons W R Preparation and assay of mammatropic hormone *Proc Soc Exper Biol & Med* 35 645 648 (Jan) 1937
- 6 — Mammalian and avian assays of hypophyseal lactogenic preparations *Endocrinology* 28 161 1 11 (Feb) 1941
- 7 Lyons W R and Catchpole H R Availability of the rabbit for assay of the hypophyseal lactogenic hormone *Proc Soc Exper Biol & Med* 31 305 309 (Nov) 1933
- 8 — Assay with the guinea pig of the lactogenic hypophyseal hormone *Proc Soc Exper Biol & Med* 31 299 301 (Nov) 1933
- 9 McShan W H and Turner C W Further purification of galactin the lactogenic hormone *Proc Soc Exper Biol & Med* 32 1655 1656 (June) 1933
- 10 — Bioassay of galactin the lactogenic hormone *Proc Soc Exper Biol & Med* 34 50-51 (Feb) 1936
- 11 Reece, R P., and Turner C W The Lactogenic and Thyrotropic Hormone Content of the Anterior Lobe of the Pituitary Gland *Columbia Univ Missouri Agr Exp Sta Res Bull* 266 1937
- 12 Riddle O Bates, R W and Dykshorn S W The preparation identification and assay of prolactin—a hormone of the anterior pituitary *Am J Physiol* 105 191 216 (July) 1933

G Mammogen I

- 1 Lewis A A and Turner C W The Mammary Hormones of the Anterior Pituitary I The Duct Growth Factor *Columbia Univ Missouri Agr Exp Sta Res Bull* 310 1939
- 2 Lewis A A Turner C W and Gomez E T Biological assay of mammary duct growth factor of anterior pituitary *Endocrinology* 33 157 164 (Feb) 1939

H Mammogen II

- 1 Mixer J P and Turner C W Biological assay of mammary lobule alveolar growth factor of anterior pituitary *Endocrinology* 29 324 329 (Sept) 1941

I Fat Metabolism Hormone

- 1 Campbell J A method of assaying the potency of anterior pituitary extracts which increase liver fat *Endocrinology* 23 692 707 (Dec) 1938

- 2 Houchin O B and Turner C W Relation of pituitary to blood lipids *Endocrinology* 24 638 644 (May) 1939
 - 3 — A method of assay for the fat metabolism hormone of the anterior pituitary *Endocrinology* 25 216 220 (Aug) 1939
- J Specific Metabolic Principle**
- 1 Billingsley I W O'Donovan D K and Collip J B The specific metabolic principle of the pituitary *Endocrinology* 24 63 68 (Jan) 1939
 - 2 O'Donovan D K and Collip J B The specific metabolic principle of the pituitary and its relation to the melanophore hormone *Endocrinology* 23 718 746 (Dec) 1938
- K Melanophore Stimulating Factor**
- 1 Abramowitz A A The role of the hypophyseal melanophore hormone in the chromatic physiology of *Fundulus* *Biol Bull* 73 134 142 1937
 - 2 — New method for biological assay of intermedin *J Pharmacol & Exper Therap* 69 156 164 (June) 1940
 - 3 Bottiger U Über das pigmenthormon I Mitteilung *Der Test, Ztschr f d ges exper Med* 101 42 47 1937
 - 4 — Über das pigmenthormon II Mitteilung Zur Darstellung und zur Frage der Duresewirkung *Ztschr f d ges exper Med* 101 48 54 1937
 - 5 — Über das pigmenthormon III Mitteilung Zur Frage der Einheitlichkeit und über die aktive Substanz alkalischer Extrakte *Ztschr f d ges exper Med* 101 55 61 1937
 - 6 Culloway N B McCormick R W and Singh N P Studies on chemistry of melanophore hormone of pituitary gland critical evaluation of a say methods *Endocrinology* 30 473-429 (Mar) 1942
 - 7 Fenn W O Active principles of the pituitary posterior lobe *J Physiol* 59 xxxv xxxvi (Oct) 1915
 - 8 Hogben L T and Slome D The pigmentary effector system VI The dual character of endocrine co-ordination in amphibian colour change *Proc Roy Soc London* 108 10-53 1911
 - 9 Jores A Untersuchungen über das Melanophorenhormon und einen Nachweis im menschlichen Blut *Ztschr f d ges exper Med* 117 266 9 1913
 - 10 Kleinholz L H and Rahn H Distribution of intermedin new biological method of assay and results of tests under normal and experimental conditions, *Anat Rec.* 76 15 17 (Feb) 1940
 - 11 Landgrebe F W and Warner H Biological assay and standardization of melanophore expanding pituitary hormone *Quart. J Exper Physiol* 33 1 15 (Jan) 1944
 - 12 Oldham F A Pharmacology and anatomy of hypophysis of *amphibian* *Anat Rec* 72 65 91 (Nov) 1915
 - 13 Teague R H Biological assay of melanophore hormone of pituitary gland *Endocrinology* 25 66, 94 (Dec) 1939
 - 14 Zondek B. and Krohn H II Hormon des Zwischenlappens der Hypophyse (Intermedin) I Die Rotfärbung der Eizelle als Testobjekt. *Klin Wchnschr* 11 43-4. (Mar) 193
 - 15 — Hormon des Zwischenlappens der Hypophyse (Intermedin) II Intermedin im Organismus (Hypophyse Gehirn) *Klin Wchnschr* 11 849 853 (May) 1932
 - 16 — Hormon des Zwischenlappens der Hypophyse (Intermedin) III Zur Chemie Darstellung und Biologie des Intermedins *Klin Wchnschr* 11 1293 1298 (July) 1932
- L Vasopressin**
- 1 Hamilton H C The pharmacological assay of pituitary preparations *J Am Pharm A* 1 1117 1119 1912
 - 2 Hamilton H C and Rowe L W Pituitary standardization *J Lab & Clin Med* 2 120 129 (Nov) 1916
 - 3 Hogben L T Schlapp W and Macdonald, A D Studies on the pituitary IV Quantitative comparison of pressor activity *Quart J Exper Physiol* 14 301 318 1924
 - 4 Kamm O Aldrich T B Grote I W Rowe L W and Bugbee M P The active principles of the posterior lobe of the pituitary gland I The demonstration of the presence of two active principles II The separation of the two principles and their concentration in the form of potent solid preparations *J Am Chem Soc* 50 573 601 (Feb) 1928
 - 5 Rowe L W Studies on oxytocin and vasopressin pressor action *Endocrinology* 11 205 212 (Mar Apr) 1929
 - 6 Simon A The secretion of the posterior lobe of the hypophysis after the administration of drugs *J Pharmacol & Exper Therap* 49 375 386 (Nov) 1933
 - 7 Swanson E E A study of the pressor method for the standardization of pituitary extract *J Lab & Clin Med* 14 754 763 (May) 1929
- M Oxytocin**
- 1 Burn J H and Dale H H On the physiological standardization of extracts of the posterior lobe of the pituitary body *Med Res Council Spec Rep.* No 69 1922
 - 2 Coon J M New method for assay of posterior pituitary extracts *Arch internat de pharm et de therap* 62 79 99 (Mar) 1919
 - 3 Dale H H and Landlaw P P A method of standardizing pituitary (infundibular) extracts, *J Pharmacol & Exper Therap* 4 75 95 (Sept) 1912
 - 4 Heller H Effect of hydrogen ion concentration on stability of antidiuretic and vasopressor activities of posterior pituitary extracts, *J Physiol* 96 331-347 (Aug) 1919
 - 5 Morrell C A, Allmark M G, and Bachman W V On biological assay of oxytocic activity of pituitary extract (posterior lobe) *J Pharmacol & Exper Therap* 70 440-449 (Dec) 1940
 - 6 Penabaz H, Prudhomme M, and Simonnet, H. Utilisation de l'utérus de certains ruminants pour de dosage du pouvoir oxytocique des extraits post hypophysaires, *J de pharm et chim.* 14 163 166, 1931
 - 7 Schubel K Über die kombinierte Wirkung von Chinin und Hypophysin auf den Uterus der lebenden Katze *Arch. f exper. Path. u. Pharmacol* 138 145-14 1915
 - 8 Sealock E R. and du Vigneaud V. Studies on the reduction of vasopressin and procaine with cyanine *J Pharmacol & Exper Therap.* 54 43-44 (Aug) 1935

- 9 Smith H H Jr Comparison of official and chicken methods for oxytocic bioassay of posterior pituitary preparations *J Pharmacol & Exper Therap* 75 342 349 (Aug) 1942
- 10 Smith R B Jr and Vos B J Jr Biological assay of posterior pituitary solution *J Pharmacol & Exper Therap* 78 72 78 (May) 1943
- 11 Thompson R F Biological assay of posterior pituitary *J Pharmacol & Exper Therap* 80 373 382 (Apr) 1944
- 12 Trendelenburg P Auswertung von Hypophysenhinterlappen präparaten am Uterus des Schafes *Arch f exper Path u Pharmacol* 138 301 305 1939
- 13 Vos B J Jr Use of latent period in assay of ergonovine on isolated rabbit uterus *J Am Pharm A (Scient Ed)* 32 138 141 (May) 1943

N Antidiuretic Factor

- 1 Boyd E M., and Mack E G Method of assaying pituitary water retention principle *Endocrinology* 26 153 159 (Jan) 1940
- 2 Burn J H Estimation of the antidiuretic potency of pituitary (posterior lobe) extract *Quart J Pharm & Pharmacol* 4 517 529 (July Sept) 1931
- 3 Gibbs O S A practical test for the antidiuretic action of pituitary *J Pharmacol & Exper Therap* 40 129 137 (Oct) 1930
- 4 Gilman A and Goodman L The secretory response of the posterior pituitary to the need for water conservation *J Physiol* 90 113 123 (July) 1931
- 5 Ham H C Reproducible diuresis and chloruresis for bioassay of antidiuretic activity *Proc Soc Exper Biol & Med* 53 210 213 (June) 1943
- 6 Hare K, Melville E V, Chambers G H and Hare H S Assay of antidiuretic material in blood and urine *Endocrinology* 36 323 331 (May) 1945
- 7 Jeffers W A, Liverzey M M and Austin J H Method for demonstrating antidiuretic action of minute amounts of pituitary in statistical analysis of results *Proc Soc Exper Biol & Med* 50 184 188 (May) 1942
- 8 Kastranek W, Molitor H and Pick E P Über die Wirkungsstärke von Hypophysenextrakten gemessen an ihren antidiuretischen Eigenschaften *Biochem Ztschr* 164 34-43 1925
- 9 Krueger V I and Kilmington T B Antidiuretic substance in urine in relation to normal and toxæmic pregnancy *M J Australia* 1 575 585 (Apr) 1940
- 10 Penau H and Simonnet H Titration biologique de l'activité antidiurétique des extraits de lobe postérieur d'hypophyse *J de pharm chim* 20 304 319 1934
- 11 Robinson F H Jr and Farr L E Relation between clinical edema and excretion of antidiuretic substance in urine *Ann Int Med* 14 42 54 (July) 1940
- 12 Silvette M Influence of post pituitary extract on water and chlorides by renal tubules *Am J Physiol* 128 747 753 (Mar) 1940
- 13 Walker A M Experiments upon relation between pituitary gland and water diuresis *Am J Physiol* 127 519 540 (Oct) 1939

IX PATHOLOGY

- 1 Altschule M D and Cooper F Changes in the pituitary gland following total thyroidectomy *Arch Path* 24 443-453 (Oct) 1937
- 2 Baker H L and Everett N B Effect of small doses of diethylstilbestrol on anterior hypophysis of immature rat *Endocrinology* 34 254 264 (Apr) 1944
- 3 Benda C Ueber den normalen Bau und einige pathologische Veränderungen der menschlichen Hypophysis cerebri *Arch f Anat u Physiol Physiol Abthlg* 3758 3 373 380 (Feb) 1900
- 4 Berblinger W Die Basophilen in Adenohypophyse und Neurohypophyse bei essentieller Hypertonie und bei Eklampsie *Endocrinology* 16 19-38 1935
- 5 — Die Korrelativen Veränderungen an der Hypophyse des Menschen *Klin Wchnschr* 7 9 12 (Jan) 1928
- 6 Bryant A R The effect of total thyroidectomy on the structure of the pituitary gland in the rabbit *Anat Rec* 47 131 145 (Nov) 1930
- 7 Chapman A and Higgins M Role of thyroid in cytologic response of pituitary to low intake of iodine *Endocrinology* 34 83 89 (Feb) 1944
- 8 Cohen H and Dible J H Pituitary basophilism associated with basophil carcinoma of anterior lobe of pituitary gland *Brain* 59 395 407 (Dec) 1936
- 9 Cramer W and Horning M S Experimental production by oestrin of pituitary tumours with hypopituitarism and of mammary cancer *Lancet* 1 247 249 (Feb) 1936
- 10 — Effect of oestrin on pituitary gland *Lancet* 1 1056 1057 (May) 1936
- 11 Crooke A C and Korenchewsky V Microscopic demonstration of hypophyses of rats normal castrated and after injection of oestrone or synthetic testicular hormone *Proc Roy Soc Med* 28 1266 1267 (July) 1935
- 12 Crooke A C. and Russell D C The pituitary gland in Addison's disease *J Path & Bact* 40 255 283 (Mar) 1935
- 13 Cushing H Further notes on pituitary basophilism *J.A.M.A* 99 281 284 (July) 1932
- 14 — Posterior pituitary activity from an anatomical standpoint *Am J Path* 9 539 548 (Sept) 1933
- 15 — Hyperactivation of neurohypophysis as pathological basis of eclampsia and other hypertensive states *Am J Path* 10 145 176 (Mar) 1934
- 16 Davis L Principles of Neurological Surgery p 181 Philadelphia Lea & Febiger 1946
- 17 Deanesley R Depression of hypophyseal activity by implantation of tablets of oestrone and oestradiol *J Endocrinol* 1 36-48 (June) 1939
- 18 Erdheim J Über Hypophysengangschwellung und Hirnchlosteatomie *Aus d Sitzungsber d Akad Wien Mathem Naturw Kl III IIB I* Dez 1904
- 19 Evans H M and Simpson M E Some effects on the hypophysis of hyper and hypothyroidism *Anat Rec* 45 215 (Apr) 1930
- 20 Forbes W Carcinoma of the pituitary gland with metastases to the liver in a case of Cushing's syndrome *J Path & Bact* 59 137 144 (Jan to Apr) 1947
- 21 Foster C L Effect of implanting tablets of synthetic oestrogens on histology and cytology

- of anterior pituitary of immature rats *J Endocrinol* 3 79 86 (Mar) 1942
- 22 Froboese C Die tuberkulöse Erkrankung der Hypophyse insbesondere über die primäre Form *Zentralbl f allg Path u path Anat* 29 145 152 (Mar) 1918
 - 23 Gardner W U Hypertrophy of interstitial cells in testes of mice receiving estrogenic hormones *Anat Rec* 68 339 347 (June) 1937
 - 24 German W J The endocrine effects of pituitary tumors *Surgery* 16 47 81 (July) 1944
 - 25 Giedosz B quoted by H B Van Dyke The Physiology and Pharmacology of the Pituitary Body, Vol 2 p 26 Chicago Univ Chicago Press 1939
 - 26 Gouley H A Basophilic adenoma of pituitary report of case of pituitary hypertension terminating in cerebral apoplexy *Ann Int Med* 8 1294 1301 (Apr) 1935
 - 27 Gregory R, and Drager G A The effect of pancreatectomy on the hypophysis *Federation Proc* 3 Part 2 p 116 (Mar) 1947
 - 28 Griesbach W E, and Purves H D Studies on experimental goitre pituitary function in relation to goitrogenesis and thyroidectomy *Brit J Exper Path* 24 174 184 (Oct) 1943
 - 29 Guyer M F and Claus P E Vascularization of the anterior pituitary gland following castration implantation of cancer tissue and thyroidectomy *Anat Rec* 67 145 156 (Jan) 1937
 - 30 Halpern S R and d'Amour F E Effects of estrin upon gonads mammary glands and hypophysis of the rat *Proc Soc Exper Biol & Med* 32 108 110 (Oct) 1934
 - 31 Hammett F S Studies of the thyroid apparatus XIII The effects of thyro parathyroidectomy and parathyroidectomy at 100 days of age on the growth of the reproductive system of male and female albino rats *Am J Anat* 32 37 51 (July) 1923
 - 32 — Studies of thyroid apparatus role of thyroid apparatus in growth of hypophysis *Endocrinology* 10 145 164 (Mar Apr) 1926
 - 33 Harrop G A Weinstein A and Marlow A Addison's disease treated with suprarenal cortical hormone (Swingle Pfaffner) *JAMA* 98 1525 1531 (Apr) 1932
 - 34 Haterius H O and Nelson W O Experimental studies of the anterior pituitary *J Exper Zool* 61 175 183 (Jan) 1932
 - 35 Heidrich L Fels E and Mathias E Testikuläre Chorionepitheliose mit Gynakomastie und mit einigen Schwangerschaftserscheinungen Gleichzeitig ein Beitrag zur Pathologie der hormonalaktiven Gewächse *Beitr z klin Chir* 150 349 384 1930
 - 36 Higgins G M Study of goitrogen promizole with reference to thyroid metabolism and blood *Am J M Sc* 210 347 362 (Sept) 1945
 - 37 Hohlweg W Corpus luteum hormon und Kastrationhypophyse *Klin Wchnschr* 14 1077 1028 (July) 1935
 - 38 Hohlweg W and Dohm M Beziehungen zwischen Hypophysenvorderlappen und Keimdrüsen *Wien Arch f inn Med* 21 337 350 (July) 1931
 - 39 Hohlweg W., and Junkmann K Über die Beziehungen zwischen Hypophysenvorderlappen und Schilddrüse *Pflügers Arch f d ges Physiol* 232 148 158 1933
 - 40 Horrax H Personal communication
 - 41 Koneff A A Effect of adrenocorticotrophic hormone on anterior pituitary of normal young male rat *Endocrinology* 34 77 82 (Feb) 1944
 - 42 Koneff A A Simpson M E Evans H M and La C H The gigantism produced in normal rats by injection of the pituitary growth hormone II Histological changes in the pituitary *Growth* 12 33 37 (Jan) 1948
 - 43 Korenchevsky V Dennison M and Simpson S L Prolonged treatment of male and female rats with androsterone and its derivatives alone or together with oestrone *Biochem J* 29 2534 2552 (Nov) 1935
 - 44 Kraus E J Handbuch der Speziellen Pathologischen Anatomie und Histologie VIII Drüsen mit innerer Sekretion in Henke F and Lubarsch O Die Hypophyse pp 810-938 Berlin Springer 1926
 - 45 — Zur Pathologie der basophilen Zellen der Hypophyse zugleich ein Beitrag zur Pathologie des Morbus Basedowi und Addisoni *Virchow's Arch f path Anat* 247 421-447 (June) 1923
 - 46 — Zur Pathologie des Morbus Addisoni (Beiträge zur Pathologie und Anatomie der Hypophyse und Nebennieren) *Beitr z path Anat u z allg Path* 78 283 90 (Sept) 1927
 - 47 — Morbus Cushing konstitutionelle Fettsucht und interrenale Virilismus Nebst Bemerkungen über den Diabetes des fettenes a barbe *Klin Wchnschr* 13 487-489 (Mar) 1934
 - 48 — Über die pathogenetische Bedeutung der Basophilie der Hypophyse in Beziehung zur Eklampsie *Med Klin* 31 1641 1642 (Dec) 1935
 - 49 Lehmann J Über das Strukturbild der Hypophyse kastrierter und nicht kastrierter Ratten unter dem Einfluss parenteral und eternal zugeführter Placentarabstrakte *Virchow's Arch f path Anat* 258 346 373 1928
 - 50 Leonard M F Chronic idiopathic hyperparathyroidism with superimposed Addison's disease in child *J Clin Endocrinol* 3 493 506 (July) 1946
 - 51 MacCallum W G and Fabian M On the anatomy of a myxoedematous idiot *Bull Johns Hopkins Hosp* 13 341 345 (Sept) 1907
 - 52 Mackenzie J B and Mackenzie C G Effect of prolonged and intermittent sulfonamide feeding on basal metabolic rate thyroid and pituitary *Bull Johns Hopkins Hosp* 74 85 97 (Feb) 1944
 - 53 MacMahon H E Close H G and Hass G M Cardiovascular renal changes associated with basophil adenoma of anterior lobe of pituitary (Cushing's syndrome) *Am J Path* 10 177 191 (Mar) 1934
 - 54 Marburg O and Wenckebach A F Über Veränderungen der Hypophyse bei Benben (Ein Beitrag zur Kenntnis der basophilen Hypophysenzellen) *Wien Arch inn Med* 29 1 24 1936
 - 55 Marine D Physiology and principal interrelations of thyroid *JAMA* 104 2250-2255 (June) 1935
 - 56 Marine D Rosen S H and Spark C Effect of iodine and desiccated thyroid on anterior pituitary of goitrous and thyroidectomized rabbits *Proc Soc Exper Biol & Med* 32 803 810 (Feb) 1935
 - 57 Martins T and Rocha A The regulation of the hypophysis by the testis and some prob

- lems of sexual dynamics (Experiments with parabiotic rats) *Endocrinology* 18 421-434 (Sept Oct) 1931
- 55 Mathias E Bericht über ein Chorionepitheliom mit deutlicher Schwangerschaftshypophyse *Arch f Gynak* 152 312-319 1933
- 56 Morrell J A., and Hart G W Studies on stilbestrol III Some effects of continuous injections of stilbestrol in normal and castrate adult rats *Endocrinology* 29 99-100 (Dec) 1941
- 57 Muller J H., and Muller C Über morphologische Veränderungen der Adenohypophyse der Ratte bei E Avitaminose *Endokrinologie* 18 369 374 (May) 1937
- 58 Nelson W O Concerning the anterior pituitary gonadal inter relations *Endocrinology* 19 187 193 (Mar Apr) 1935
- 59 — Effect of oestrin and gonadotropic hormone injections upon hypophysis of the adult rat *Proc. Soc Exper Biol & Med* 32 452 454 (Dec) 1934
- 60 Nelson W O and Gallagher T F Some effects of androgenic substances in the rat *Science* 84 230-232 (Sept) 1936
- 61 Niepce, B *Traité du goitre et du crétinisme* p 43 Paris Baillière 1851
- 62 Nitzescu I F., and Boitiano S Les effets des fortes doses de vitamine D sur la structure histologique des glandes à sécrétion interne *Compt rend Soc de biol* 121 1533 1535 (Feb) 1936
- 63 Noble R L Functional impairment of anterior pituitary gland produced by synthetic oestrogenic substance 4 4 dehydroxy a B diethylstilbene *J Physiol* 94 17 183 (Oct) 1938
- 64 — Effects of synthetic oestrogens and carcinogens when administered to rats by subcutaneous implantation of crystals or tablets *J Endocrinol* 1 216 229 (Sept) 1939
- 65 de Quervain F., and Wegelin K *Der endemische Kretinismus* pp 101 103 Berlin Springer 1936
- 66 Rasmussen A T The relation of the basophilic cells of the human hypophysis to blood pressure *Endocrinology* 20 673 678 (Sept) 1936
- 67 — The weight of the principal components of the normal hypophysis cerebri of the adult human female *Am J Anat* 55 253 275 (Sept) 1934
- 68 Reece J D Koneff A A and Wainman P Cytological differences between castration and thyroidectomy basophils in the rat hypophysis *Essays in Biology* pp 473-482 Berkeley Univ California Press 1943
- 69 Reveno W E Effect of thioracal on human tissues *J Clin Endocrinol* 5 403-406 (Nov) 1945
- 70 Rogowitsch N Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse *Beitr z path Anat u z allg Path* 4 453-470 1888 1889
- 71 Schoneemann A Hypophysis und thyreoidea *Virchow's Arch f path. Anat* 129 310 336 (Aug) 1892
- 72 Schoeller W Dohrn M and Hohlweg W Die Überlegenheit des weiblichen Hormons in seiner Wirkung auf die männliche und weibliche Kastraten hypophyse gegenüber männlichen Hormonen *Klin Wchnschr* 15 1907 1908 (Dec) 1936
- 73 Schultze W II Todliche Menorrhagie in einem Falle von Thyreoplasie mit Hauptzellendnom der Hypophyse *Virchow's Arch f path Anat* 216 443-452 (June) 1914
- 74 Selye H., Browne J S L and Collip J B Effect of large doses of progesterone in female rat *Proc Soc Exper Biol & Med* 34 472 474 (May) 1936
- 75 Selye H Collip J B., and Thomson D L Effect of oestrin on ovaries and adrenals *Proc Soc Exper Biol & Med* 32 1377 1381 (May) 1935
- 76 Severinghaus A E Cytology of pituitary gland A Research Nerv & Ment Dis *Proc* 17 69 117 1938
- 77 — Cellular changes in the anterior hypophysis with special reference to its secretory activities *Physiol Rev* 17 556 588 (Oct) 1937
- 78 — Pituitary Gland pp 69 117 Baltimore Williams & Wilkins 1938
- 79 — Some interrelationships of pituitary gland and thyroid *West J Surg* 50 371 381 (Aug) 1947
- 80 Severinghaus A E and Thompson K W Cytological changes induced in hypophysis by prolonged administration of pituitary extract *Am J Path* 15 391-412 (July) 1939
- 81 Sheehan H L Simmonds disease due to post partum necrosis of the anterior pituitary *Quart J Med* 32 277 290 (Oct) 1939
- 82 Smelser G K Effect of thyroidectomy on reproductive system and hypophysis of adult male rat *Anat Rec* 74 7 16 (May) 1939
- 83 Smith P E and McDowell C An hereditary anterior pituitary deficiency in the mouse *Anat Rec* 46 249 257 (Aug) 1930
- 84 Soffer L J Diseases of the Adrenals p 56 Philadelphia Lea & Febiger 1946
- 85 Spark C Relation between basophilic invasion of the neurohypophysis and hypertensive disorders *Arch Path* 19 473 501 (Apr) 1935
- 86 — Structure of human anterior pituitary gland after administration of estrogenic hormones *J Clin Endocrinol* 3 367 374 (June) 1943
- 87 Stein K F and Lisle M Gonad stimulating potency of pituitary of hypothyroid young male rats *Endocrinology* 30 16 24 (Jan) 1942
- 88 Steiner P E and Dunham L J The anterior pituitary gland in women with carcinoma of the mammary gland with report of a case of chromophobe adenoma *Am J Path* 19 1031 1042 (Nov) 1943
- 89 Susman W Adenoma of the pituitary with special reference to pituitary basophilism of Cushing *Brit J Surg* 22 539 544 (Jan) 1935
- 90 Wegelin K Zur Kenntnis der Kacheua thyreopriva *Virchow's Arch f path Anat* 254 689 709 1925
- 91 Weil A and Zondek M Histopathology of pituitary of white rat injected with follicular hormone *Endocrinology* 25 114 122 (July) 1939
- 92 Wolfe J M Reaction of ovaries of mature female rats to injections of oestrin *Proc Soc Exper Biol & Med* 32 757 759 (Feb) 1935
- 93 Wolfe J M and Hamilton J B Comparative action of testosterone compounds of esters and of combinations of testosterone

- compounds and esterone on the anterior hypophysis, *Endocrinology* 21 603 610 (Sept) 1937
- 97 — Response of anterior pituitary of immature castrated rat to testosterone and related compounds *Proc Soc Exper Biol & Med* 36 307 310 (Apr) 1937
 - 98 — Action of male sex hormone with and without estrin in the female rat *Proc Soc Exper Biol & Med* 37 189 193 (Oct) 1937
 - 99 Wolfe J M and Wright A W Histologic effects induced in anterior pituitary of rat by prolonged injection of estrin with particular reference to production of pituitary adenomata *Endocrinology* 23 200 210 (Aug) 1938
 - 100 Zeckwer I T Davidson L W Keller T H and Livingston C S The pituitary in experimental cretinism I Structural changes in the pituitaries of thyroidectomized rats *Am J M Sc* 190 145 157 1935
 - 101 Zondek B Effect of prolonged administration of estrogen on uterus and anterior pituitary of human beings *JAMA* 114 1850 1854 (May) 1940
 - 102 — Clinical and Experimental Investigations on the General Functions and their Hormonal Regulations pp 17 116 143 Baltimore Williams & Wilkins 1941
 - 103 Zondek H The Diseases of the Endocrine Glands ed 4 p 322 Baltimore Williams & Wilkins 1944
- ### XIII EXAMINATION OF PATIENT
- 1 Best C H and Taylor N B The Physiological Basis of Medical Practice p 556 Baltimore Williams & Wilkins 1945
 - 2 Cantarow A and Trumper M Clinical Biochemistry p 239 Philadelphia Saunders 1949
 - 3 Carter A C and Robbins J Ue of hypotonic saline infusions in differential diagnosis of diabetes insipidus and psychogenic polydipsia *J Clin Endocrinol* 7 753 766 (Nov) 1947
 - 4 Fulton M N and Cushing H The specific dynamic action of protein in patients with pituitary disease *Arch Int Med* 50 649 667 (Nov) 1932
 - 5 Grant F C Ventriculography *Am J Roentgenol* 18 264 269 (Sept) 1937
 - 6 Jefferson G On the saccular aneurysms of the internal carotid artery in cavernous sinus *Brit J Surg* 26 267 302 (Oct) 1938
 - 7 McGavack T H Benjamin J W and Liebowitz S Diabetes insipidus *Arch Neurol & Psychiat* 44 867 878 (Oct) 1940
 - 8 McGavack T H Boyd L J and Gelvin P Experimental modification of water and salt output in patients with diabetes insipidus *J Clin Endocrinol* 2 551 559 (Sept) 1942
 - 9 Moniz E Intracranial aneurysm of the right internal carotid artery made visible by cerebral arteriography *Rev oto-neuro-ophth* 11 746 748 1933
 - 10 Ryncarson E H and Kepler E J Diseases of the pituitary gland *M Clin North America* 24 953 980 (July) 1940
 - 11 Soffer L J Lesnick G Sorkin S Z Sobotka H H and Jacobs M The utilization of intravenously injected salt in normals and in patients with Cushing's syndrome before and after administration of desoxycorticosterone acetate *J Clin Investigation* 23 51 54 (Jan) 1944
 - 12 Paschke K E Hypophysis in protein metabolism Is pituitary factor active in protein metabolism identical with growth hormone? *Endocrinology* 23 368 370 (Sept) 1938
 - 13 Poppen, J L Ventricular drainage as a valuable procedure in neurosurgery report of satisfactory method *Arch Neurol & Psychiat* 50 587 589 (Nov) 1943
 - 14 — Aid of arteriograms in diagnosis and treatment of intracranial aneurysm *Radiology* 52 347 352 (Mar) 1949
- ### XIV THE SELLA TURCICA
- 1 Abt I A *Pediatrics* Vol 1 p 378 Philadelphia Saunders 1923
 - 2 Bokelmann O Die spezielle Anatomie der Sella turcica und ihre klinische Bedeutung für die Erkennung der Hypophysengröße zugleich ein Beitrag zur Frage der Beziehungen der Hypophysengröße sowie Größe und Form der Sella zum anatomischen und funktionellen Hypophysismus *Fortschr a d Geb d Röntgenstrahlen* 49 364 396 (Apr) 1934
 - 3 Boyce, R and Beadles C G A further contribution to the study of the pathology of the hypophysis cerebri *J Path & Bact* 1 359 383 1891 1893
 - 4 Brill L Vergleichende Messungen der Sella turcica im Kindesalter *Monatsschr f Kinderh* 57 1 6 (Feb) 1933
 - 5 Comte L Contribution à l'étude de l'hypophyse humaine et de ses relations avec le corps thyroïde *Beitr z path Anat u z allg Path* 23 90 110 1898
 - 6 Costello R T Subclinical adenoma of the pituitary gland *Am J Path* 12 205 216 (Mar) 1936
 - 7 Davenport C B and Renfro O Adolescent development of sella turcica and frontal sinus based on consecutive roentgenograms *Am J Roentgenol* 44 665 679 (Nov) 1940
 - 8 Erdheim J and Stumm M Ueber die Schwangerschaftsveränderung der Hypophyse *Beitr z path Anat u z allg Path* 46 1 137 1909
 - 9 Fitzgerald D P Pituitary fossa and cranial skull measurements *J Anat. & Physiol* 44 231 233 (Apr) 1910
 - 10 Gibson W S The topography of the hypophysis cerebri *Surg Gynec & Obst* 15 199 204 (Aug) 1912
 - 11 Giordani A J Sur le diagnostic des tumeurs de l'hypophyse par la radiographie *Paris* 1906
 - 12 Gordon M B and Bell A L A roentgenographic study of the sella turcica in normal children *New York State J Med* 22 54 58 (Feb) 1922
 - 13 — A roentgenographic study of sella turcica in abnormal children *Endocrinology* 9 265 276 (July Aug) 1925
 - 14 Gundobin N P Die Besonderheiten des Kindesalters pp 229 231 Berlin Allgemeine Medizinische Verlagsanstalt G m b H 1912
 - 15 Haas L Erfahrungen auf dem Gebiete der radiologischen Selladiagnostik A Allgemeiner Teil *Fortschr a d Geb d Röntgenstrahlen* 419 422 B Spezieller Teil 469 494 (Apr) 1925
 - 16 Hare H F Personal communication

- 17 Hare H F., Newcomb R B., Taft G H., Saltzman F A, Silveus E, Musulin N and Hurxthal L M Unpublished data
- 18 Hare H F, Silveus F., and Smedal M I Roentgenologic diagnosis of pituitary tumors Radiology 57 193 193 (Feb.) 1949
- 19 Heublein W Some observations concerning the hypophysial fossa Am J Roentgenol 56 299 319 (Sept.) 1946
- 20 Howe H S Normal and abnormal variations in pituitary fossa Neurological Bull 2 233 (June) 1919
- 21 Hrdlicka A Dimensions of the normal pituitary fossa or sella turcica in the white and the negro races Arch Neur & Psychopath 1 No 4 679 698 1898
- 22 Hurxthal L M Pituitary tumor S Clin North America 27 530 534 (June) 1947
- 23 Hurxthal L M and Younghusband O Diagnosis of hypopituitarism as associated with chromophobe tumor (presumed or verified) Radiology 52 179 185 (Feb.) 1949
- 24 Jewett C H Teleroentgenography of sella turcica with observations on 100 normal cases Am J Roentgenol 7 352 (July) 1920
- 25 Kovács Ákos Untersuchungen über die Sella turcica nach Haas bei Kindern und bei Erwachsenen Fortschr a d Geb d Röntgenstrahlen 50 469-482 (Nov.) 1934
- 26 Lucien M Le poids, les dimensions et la forme générale de l'hypophyse humaine aux différents âges de la vie, Comptes rendus de l'association des Anatomistes 13 147 159 1911
- 27 Maier O Die Grosse und Form der Sella turcica in Abhängigkeit von Grosse und Form des Schädels und die Häufigkeit von Sella varianten Med Diss München pp 1 25 1936
- 28 Mategka Jindrich Graphic representation of the inside of the skull with special reference to the pituitary fossa Am J Phys Anthropol 3 397-402 (Oct-Dec) 1920
- 29 Melodesi Gastone and Pansadoro Enzo Proposta di un metodo radiografico per calcolare il volume della sella turcica (nel teschio e nel normale) Policlino (Sezione Medica) XVI Anno XLIV No 11 pp 533 545 (Nov.) 1937
- 30 Nippce H Traité du goitre et du crétinisme p 48 Paris Baillière 1851 1852
- 31 Ottaviani G Ricerche anatomoradiografiche e volumetriche sui rapporti fra sella turcica ed ipofisi umana Arch Ital di anat e di embriol 40 194 214 1938
- 32 Pancoast H K, Pendergrass E P and Schaefer J P The Head and Neck in Roentgen Diagnosis p 591 Springfield Thomas 1940
- 33 Iruekt B S On the dimensions of the hypophysial fossa in man Am J of Phys Anthropol 11 205 222 (Jan-Mar) 1928
- 34 Rasmussen A T Quantitative study of human hypophysis cerebri or pituitary body Endocrinology 8 509 524 (July) 1924
- 35 Renert H Beitrag zur roentgenologischen Selladiagnostik Fortschr a d Geb d Röntgenstrahlen 35 553 573 (Dec) 1916
- 36 Royster L T., and Rodman N F Size of sella turcica in relation to body measurements Tr Am Pediat Soc 34 246 266 1922
- 37 Sartorius W Über die Möglichkeit einer objektiven Grossenbestimmung der Sella turcica im Kindesalter Monatschr f Kinderh 45 259 267 1929
- 38 Scheuermann H The roentgenological picture of the normal and pathologic sella turcica Acta radiol 13 404-430 1932
- 39 Schonemann A Hypophysis und Thyreoidea Arch f path Anat u Physio u f klin Med 129 310 336 1892
- 40 Simmonds H Zur Pathologie der Hypophysis Verhandlungen der Deutschen Pathologischen Gesellschaft 17 208 212 1914
- 41 Steiert Anton Über die kindliche Sella turcica ihre normale Entwicklung und ihr Verhalten bei einer Reihe von Abnormen Zuständen Fortschr a d Geb d Röntgenstrahlen 38 339 343 (Aug.) 1928
- 42 Thom W Untersuchungen über die normale und pathologische Hypophysis cerebri des Menschen Arch fur Mikroskopische Anatomie 57 632 652 (Feb.) 1901
- 43 Von Wolfgang Weiser Zur Entwicklung der kindlichen Sella unter normalen und pathologischen Verhältnissen Wiener Klin Wchnschr 46 1220 1224 (Oct.) 1933
- 44 Younghusband O and Hurxthal L M Unpublished data
- 45 Ziskin T Observations on the hypophysial area in hypertension Radiology 53 406 409 (Sept.) 1949



FIG 20 ADULT PITUITARY GLAND Horizontal section ($\times 78$) showing relative size of anterior (1) and posterior (2) lobes (S P Hicks and W A Meissner)

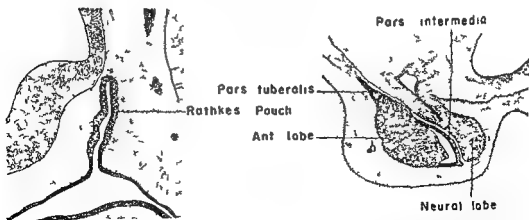


FIG 21 EMBRYOLOGIC DEVELOPMENT OF THE PITUITARY (Left) Sagittal section through hypophysis region of a 10.5 mm human embryo Nasal end at left (Right) Sagittal section through hypophysis region of a 55 mm human embryo Nasal end at left (Atwell W J The development of hypophysis cerebri in man with special reference to pars tuberalis Am J Anat 37 159)

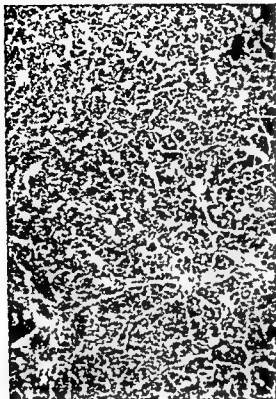


FIG 22 PITUITARY GLAND Normal anterior pituitary gland in an adult male. Note sinusoidal arrangement of cells (x 72)



FIG 23 MALIGNANT ADENOMA OF THE ANTERIOR PITUITARY Section from a partially removed tumor in an underdeveloped 15 year-old boy who complained of headache. Weight 83 lbs Height 58 in Bone age 17 years Large sella turcica (2.5 sq mm) Complete blindness in left eye Quadrant defect in right. Recurrence of symptoms several months after operation. Marked improvement with roentgen therapy. Note the large cells with multiple or very large nuclei and occasional mitoses

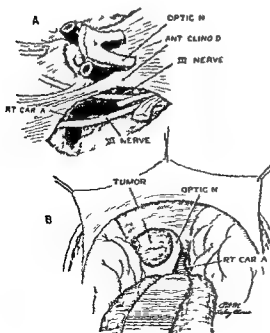


FIG 24 ANATOMY OF THE SELLAR AREA (A) Anatomic relationships of optic chiasm third and sixth cranial nerves and internal carotid arteries to sella turcica are illustrated. The cut stalk of the pituitary gland is seen under the chiasm (B) An expanding pituitary tumor is shown spreading the chiasm. Note position of right carotid artery (A and B) and the potentialities of pressure phenomena with an aneurysm. One effect detectable only in roentgenograms of optic foramina is erosion of the floor under the optic nerve between the anterior clinoid and the dorsum sellae

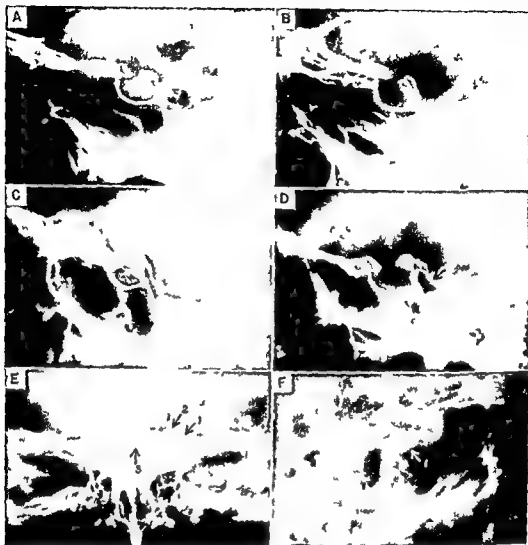


FIG 25 NORMAL SELLA TURCICAS AS SHOWN BY ROENTGENOGRAPHY (A) Lateral view of a normal sella (B) Slightly oblique view (other film of stereoscopic set) showing both anterior and posterior clinoid processes (C) A bridged sella = of no endocrine significance (D) Calcification of petroclinoid ligament (arrow) a normal finding when present (E) PA view showing anterior clinoids (1) dorsum and posterior clinoids (2) and planum sphenoidale (3) (F) Arteriogram of a normal skull (1) floor of sella (2) internal carotid artery

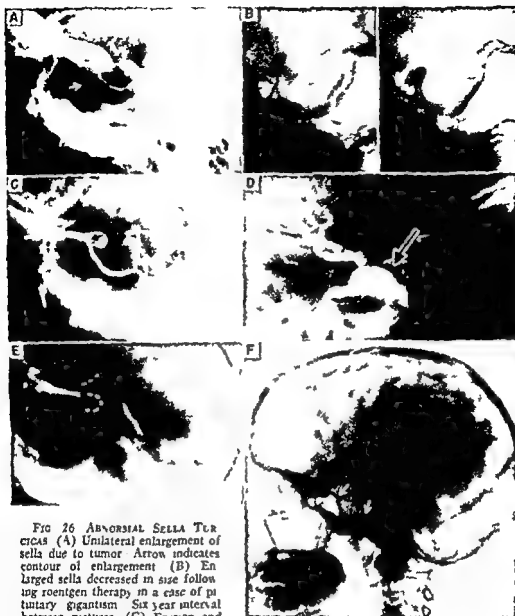


FIG 26 ABNORMAL SELLA TURCICAS (A) Unilateral enlargement of sella due to tumor. Arrow indicates contour of enlargement. (B) Enlarged sella decreased in size following roentgen therapy in a case of pituitary gigantism. Six year interval between pictures. (C) Erosion and nonvisualization of one anterior clinoid process (arrow) due to aneurysm verified by arteriogram. (D) Arteriogram demonstrating aneurysm of internal carotid artery which eroded one anterior clinoid. (E) Elevation of anterior clinoid due to aneurysm. (F) Enlargement of sella with erosion and nonvisualization of all clinoid processes due to chronic internal hydrocephalus. Note also scalloping of skull due to chronic pressure.

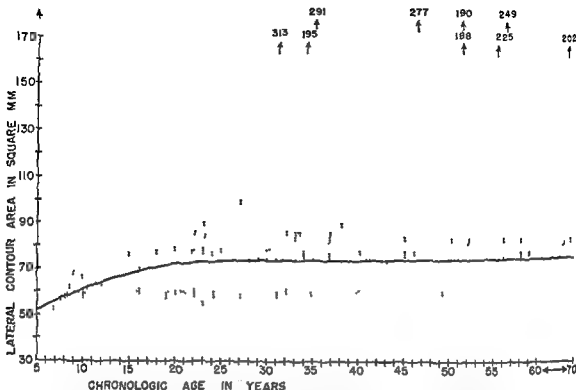


CHART 11 MEASUREMENT OF LATERAL AREAS OF SELLA TURCICA Distribution according to size and age of 671 consecutive roentgenograms A large number were measured by low time including all those before 10 years of age which proved to be too tedious The rest were estimated by sella meter This accounts for the tendency of the results to fall into groups The dots with numbers and arrows were well above 1.0 sq mm and represented for the most part tumors which were clinically significant The black line indicates averages for each 5 year group the wide variation is to be noted (From unpublished data of Drs Hare H F Newcomb R B, Taft G H Saltzman F A Silveus E Musulin N and Hurxthal L M)

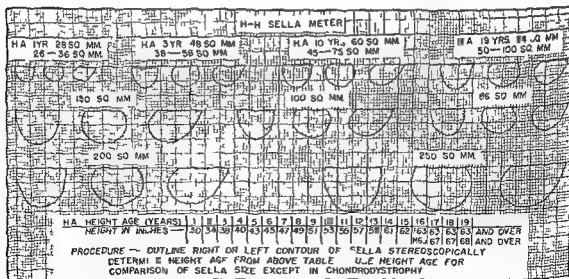


CHART 12 SELLA METER Average lateral contour areas at different ages The above arrangement is used for determining quickly the size of sella when imprinted on transparent cellophane (known as the sella meter—Hurxthal & Hare May be procured from Ansco Binghamton N Y) (Hare H F Silveus E and Smedal M I Roentgen Diagnosis of Pituitary Tumor Radiology 52 193)

PITUITARY—CLINICAL HYPOPITUITARISM

INTRODUCTION

I DEFINITION

GENERAL—A deficiency or absence of one several or all hormones of the anterior lobe of the hypophysis

II CLINICAL (HORMONAL) CLASSIFICATION

A INTRODUCTION

- 1 Different combinations of hormonal deficiency may exist
- 2 Intermediate syndromes between well defined clinical types are possible
- 3 Hypersecretion of several factors may be found in presence of hyposecretion of others i.e. pituitary gigantism

B PREPUBERAL ANTERIOR PITUITARY DEFICIENCIES

- 1 Apituitarism (panhypopituitarism)
 - a Complete absence of anterior pituitary hormones
 - b Example—Simmonds' disease
- 2 Hypopituitarism
 - a Essentially a reduction in all anterior pituitary hormones
 - b The difference between hypopituitarism and apituitarism is chiefly a matter of degree and cannot always be determined in any one case
 - c The following syndromes consist mainly of gonadotropic and growth hyposecretion with a lesser deficiency of other pituitary hormones
 - d These conditions are closely allied if not identical
 - (1) Pituitary dwarfism (see Figs 29 and 30)
 - (2) Frohlich's syndrome (adiposogenitodystrophy (see Fig 27))
 - (3) De la Cour-Lorain-Levi infantilism (see Fig 28)^{20 7}
 - (4) Ateliosis (Greek derivative)

(5) Nanism (Latin derivative)²⁸

(6) Pseudo-dwarfism⁹

e Growth and gonadotropic hypofunction

(1) Retarded growth and hypogonadism without evidence of other hormonal deficiency occur occasionally

(2) Undoubtedly, these cases might be classified under above syndromes (see 5 \I)

3 Hypogonadotropic deficiencies

a Hyposecretion of one or both of the following

(1) Follicle stimulating hormone (FSH)

(2) Luteinizing hormone (LH)

b Examples (all may be transient with eventual recovery)

(1) FSH deficiency—eunuchoidism

(2) FSH and LH deficiencies—eunuchoidism

(3) LH deficiency—adiposogenital dystrophy or hypogonadism (as described by McCullagh⁶⁴)

C POSTPUBERAL ANTERIOR PITUITARY DEFICIENCIES

1 Apituitarism

a Complete absence of all the anterior lobe hormones

b Example—Simmonds' disease

2 Hypopituitarism—hypofunction involving most or all anterior pituitary hormones

3 Unihormonal deficiencies predominantly

- a Hypogonadotropic — FSH and/or LH deficiency (see 45 \ B 3 47 \I)

b Pituitary myxedema (hypothyroid deficiency) (see 6)

c Pituitary Addison's disease (hypoadrenocorticotrophic deficiency) (see 7)

SECTION 3

PREPUBERAL HYPOPITUITARISM

I DEFINITION	A condition resulting from diminished secretion of the anterior pituitary hormones (hypopituitarism), generally including all of them, but especially the gonadotropic and growth factors
II APPEARANCE	A well proportioned normal looking individual with retarded growth and sexual development (see Figs 27 30, 34 36, 38 40)
III AGE	Any before puberty
IV SEX	No predominance of either
V MENTAL DEVIATIONS	
A INTELLIGENCE	Normal I Q , occasionally below normal if there is pressure from the pituitary tumor or when associated with a primary mental deficiency ^{4 6 10 14 36 78}
B RESPONSIVENESS	Usually, alert, rarely retarded, impish, emotional
C OTHER ABNORMALITIES	No deviation from normal psyche immature, and mild psychoses in some
VI PHYSICAL STATUS	
A NUTRITION	
1 Weight	From undernourished to obese ^{6 78}
2 Fat distribution	Female contours in the male (absence of male sex hormone) not remarkable in females prominent mons pubis especially in male
B HEIGHT	Proportionate dwarfism, final stature dependent on age of onset, duration and rate of growth retardation
C EXTREMITIES	
1 Upper	Proportionate to body size
a Hands	Proportionate to development
b Fingers	Proportionate
c Span	Normal for height
2 Lower	Proportionate to body size
■ Feet	Match rest of size
b Toes	Proportionate
D SPINE	Normal
E INTEGUMENT	
1 General	
a Texture	Normal or smooth later wrinkled geroderma nails thin and underdeveloped
b Temperature	Subnormal
■ Moisture	Normal or decreased
d Eruptions	None
e Pigmentation	Brown freckles moles hemangiomas frequent
f Color	Eventually pallor

2 Hair	
a Head	Fine sparse or abundant
b Facial	None
c Axillary	Absent or slight amount, delayed in appearance
d Pubic	Absent or slight amount delayed in appearance
e Body	Variable
F HEAD	
1 Shape and size	Proportionate to body size
2 Facial expression	Infantile except late in disease
3 Eyes	
a General	Normal, occasionally ptosis and/or ophthalmoplegia squint ¹³
b Fundi	Normal papilledema or optic atrophy ⁷
c Visual	
(1) Fields	Normal or restricted if tumor is the cause (craniopharyngioma) ²³
(2) Acuity	Normal unless tumor pressure, may have complete loss
4 Ears and nose	Proportionate to face smell may be impaired or absent
5 Mouth and throat	
a General	Normal
b Teeth	Normal ⁴⁰ may have widely spaced upper incisors and abnormal development of lateral incisors, delayed decidual extrusion
G NECK	
1 General	Proportional to build
2 Thyroid	Barely palpable if at all
H CHEST	
	Narrow 'miter shaped'
I HEART AND PERIPHERAL VESSELS	
1 Heart	Not remarkable may be hypoplastic
2 Rate and rhythm	Normal or bradycardia
3 Blood pressure	Normal or slightly decreased ^{1 31 4 7}
4 Peripheral arteries and veins	Normal
5 Vasomotor	See skin
J BREASTS	
1 Male	Normal no actual primary gynecomastia
2 Female	Underdeveloped
K ABDOMEN	
	Often potbellied ³⁷
1 Liver	Not palpable (see 92 V D 2a)
2 Spleen	Not palpable
3 Hernia	None
4 Tumor	None
L GENITALIA	
1 Male	
a Penis	Small
b Testes	Small or undescended flabby consistency but may feel normal for developmental stage ^{39 8 67 70 8}
c Prostate	Small
2 Female	
a External	Retarded
b Internal	Atrophic

M NEUROMUSCULAR

- | | |
|------------------|--|
| 1 Muscles | Not well developed |
| 2 Gait | Matches height, may be ataxic |
| 3 Body movements | Normal, some very graceful others awkward |
| 4 Tremor | None |
| 5 Paresthesias | None |
| 6 Reflexes | Normal may be increased in presence of tumor |

N SPEECH

Normal

VII LABORATORY DATA—see 5 VII**VIII ROENTGENOLOGIC FINDINGS****A SKULL (see Figs 31, 33 and 35)**

- | | |
|-----------------|---|
| 1 Cranial vault | Normal or thin |
| 2 Sella turcica | Normal small or enlarged if tumor or cyst is present, suprasellar calcification possible erosion of clinoids, separated sutures ^{13 1 71 1 20 G. 8 87} |
| 3 Mandible | Disproportionate to maxilla ¹³ |
| 4 Sinuses | Poorly developed |
| 5 Teeth | Normal dental age, may be retarded ¹⁰ |

B EPIPHYSEAL STATUS (bone age)

Retarded usually at any age may be normal if very recent onset, epiphyses may show necrosis or remain cartilaginous may close late if treated development of osseous nuclei is delayed (see Figs 31 37 and 42)^{1 8 10 14 15 37 39 0 11 31}

C LONG BONES

Proportionate to body size

D VERTEBRAE

Normal may be osteoporotic

E BONE TEXTURE

Appears normal

F MISCELLANEOUS

Nothing additional

IX ETIOLOGY (see 92 IV V)**A UNKNOWN****B CONGENITAL—Diagnosis by**

- 1 Exclusion
- 2 Family history

C TUMOR (see 3 V)

- 1 Pituitary
- 2 Hypothalamic

D NUTRITIONAL AND/OR METABOLIC CHANGES—Probably action through pituitary in many cases**E TRAUMA^{67 75}****F HYDROCEPHALUS****G INFECTIONS**

- 1 Syphilis
- 2 Meningitis
- 3 Encephalitis
- 4 Others

X PATHOLOGY^{1 4 14 3 30 39 67 70 78}**A Gross**

- 1 Pituitary^{9 70 71 6}
 - a Normal^{11 6}
 - b Teratoma
 - c Craniopharyngioma (adamantinoma of craniopharyngeal duct) (see Fig 29)^{8 11 17 8 35 9}
 - d Other tumors found
 - (1) Angiomatous⁴⁷
 - (2) Benign chromophobe⁴
 - (3) Basophil adenoma⁵⁴
 - (4) Malignant adenoma (anterior lobe) (see Fig 23)
 - (5) Suprasellar types⁸
 - e Cholesteatoma
 - f Colloid cystic degeneration⁴³
 - g Necrosis may be embolic⁶⁹

- h Hypoplasia or atrophy with fibrotic sclerosis^{12, 23}
 - i Hemorrhage^{6, 7}
 - j Abscess¹
 - 2 Thyroid^{29, 41}
 - Normal
 - Hypoplasia
 - 3 Adrenals
 - a Normal
 - b Hypoplasia²⁹
 - 4 Gonds^{8, 49}
 - a Normal
 - b Small
 - 5 Thymus^{49, 71}
 - a Small
 - b Enlarged
 - 6 Cerebral lesions
 - Infundibular tumor
 - b Hydrocephalus⁷²
 - Glioma
 - d Endothelioma
 - 7 Other organs—general splanchnomericia
- B Microscopic Pituitary—different lesions see above and 2 IX B¹¹

XI PATHOLOGIC PHYSIOLOGY

- A GROWTH FACTOR
 - 1 Hyposecretion rarely ceases
 - 2 Level of serum phosphorus may reflect degree of hormonal function
- GONADOTROPINS
 - 1 Reduction or absence of secretion
 - 2 Retardation and cessation of sexual development
- C THYROTROPIN
 - 1 Variable degrees of decreased secretion
 - 2 Mental deterioration or cretinism is rarely observed
- D ADRENOCORTICOTROPIN
 - 1 Amount is reduced (by inference)
 - 2 Addisonianlike symptoms are unusual
 - 3 The higher degree of thyroid function in Addison's disease may be responsible for the frequent acute crises in that disease as compared with their uncommon occurrence in hypopituitary states
 - 4 Water test may be positive however there is little evidence of faulty salt metabolism
 - 5 N and S hormones are balanced at a decreased level

E COMMENT

- 1 General physical and mental activity seem less affected in hypopituitary dwarfs than in adults
- 2 This may be due to a greater capacity of the endocrine glands to function at a low level independently of the pituitary during childhood (see Protocols 3 I to IV)
- 3 The following may play a role
 - a Daily caloric intake
 - b Appetite
 - c Utilization of protein⁶⁸
 - (1) Ingestion of gelatine produces a normal rise in blood amino acids in pituitary dwarfs
 - (2) With severe pituitary cachexia on the other hand there is an abnormal rise in blood amino acids suggesting faulty anabolism
- d Hypothalamic involvement

XII SYMPTOMATOLOGY

A OF TUMOR AND/OR INTRACRANIAL PRESURE

- 1 Headache
 - a Location
 - (1) Frontal
 - (2) Bitemporal
 - b Vague
 - c Persistent
 - d Severity variable
- 2 Visual disturbances
 - a Scotoma
 - b Blindness one or both eyes
 - c Amblyopia
 - d Diplopia
 - e Squint
 - f Ptosis
 - g Visual fields
 - (1) Restricted
 - (2) Hemianopsia
 - (a) Unilateral
 - (b) Bilateral
- 3 Nasal complaints
 - a Anosmia (in some)
 - b Spinal fluid seepage through nose or nasopharynx
 - c Epistaxis
- 4 Deafness
- 5 Vertigo
- 6 Insomnia

- 7 Somnolence
- 8 Lethargy
- 9 Weakness
- 10 Mental effects
 - a Aberrations
 - b Stupor
 - c Irritability
 - d Psychosis
- 11 Speech difficulties
- 12 Neurologic changes
- 13 Convulsive seizures

B GROWTH RATE IS RETARDED

C SECONDARY SEX DEVELOPMENT IS DELAYED

D GASTRO INTESTINAL

- 1 Anorexia may be severe at times
- 2 Polydipsia (diabetes insipidus)
- 3 Vomiting, may be projectile
- 4 Constipation

E GENITO URINARY—Polyuria (diabetes insipidus) (see Fig 34)

F MISCELLANEOUS

- 1 Cold sensitivity
- 2 Pallor
- 3 Fatigability

XIII DIAGNOSIS

A RETARDATION OF

- 1 Growth rate (see Fig 32)
- 2 Height age
- 3 Bone age
- 4 Sexual development

B LABORATORY DATA

- 1 Relative lymphocytosis of childhood persists⁴⁹
- 2 Plasma cholesterol may be increased
- 3 Serum inorganic phosphorus below 4.5 mg % at any age depending on rate of growth
- 4 Sugar tolerance usually increased
- 5 17 ketosteroids are^{27 34 49}
 - a Absent
 - b Very low

XIV DIFFERENTIAL DIAGNOSIS

A DWARFISM—Eliminate other forms of dwarfism—see 92 V, 93 95

B HYPOGENITALISM (up to 14 or 15 years of age, during usual pubescent and adolescent periods⁴⁹) (see 1 VI)

1 Definition

- a Hypogenitalism in the male as used herein indicates a disproportionate genitalia in relation to height age of the individual
- b In the female this appraisal is not easy

2 Comment

- a It is often difficult to differentiate clinically the various types of hypogenitalism
- b When special facilities for study are not available, observations for a year or so may settle the diagnosis
- c The following outline should serve to evaluate the significance of hypogenitalism

3 Types

- a Pseudohypogenitalism (male)
 - (1) Genitalia submerged, due to excess obesity during or before pubescence normal outcome eventually
 - (2) Normal range for the following
 - (a) Height age (often increased)
 - (b) Bone age
 - (c) Growth rate
 - (d) Breast development, enlargement is not uncommon
 - (e) Testicular size
 - (f) Urinary FSH
 - (g) 17 ketosteroids
- b Delayed puberty, male and female and hypogenitalism
 - (1) Transient disorder with or without obesity
 - (2) Normal range for the following
 - (a) Height age
 - (b) Bone age
 - (c) Growth rate
 - (d) Breast development
 - [1] Male—enlargement is common
 - [2] Female—delayed
 - (e) 17 ketosteroids
 - (3) Menarche—delayed
 - (4) Testes and penis—pubescent size
 - (5) Urinary FSH
 - (a) Normal
 - (b) Increased
- c True primary hypogenitalism due to testicular or ovarian disease
 - (1) Etiology—see 48 IX, 65 IX

- (2) Synonyms
 - (a) Primary hypogonadism
 - (b) Primary hypopituitarism
 - (c) FSH positive eunuchoidism
- (3) Height age—normal
- (4) Bone age is increasingly retarded as age approaches usual time of epiphyseal closure (18 for boys, 17 for girls)
- (5) Growth rate—normal
- (6) Span
 - (a) Increases over height beginning between the ages of 12 to 14
 - (b) Becomes greater as growth proceeds unless treated
- (7) Breasts
 - (a) Male—may enlarge
 - (b) Female—development may be
 - [1] Absent
 - [2] Slight
- (8) Testes
 - (a) Small
 - (b) Flabby
 - (c) Minuscule
- (9) Amenorrhea (primary)
- (10) Urinary FSH
 - (a) Increased
 - (b) Progressively greater amounts in subsequent years
- (11) 17 ketosteroids
 - (a) Low for age
 - (b) Increased possibly due to adrenal hyperplasia
- d True secondary hypogonadism (see 47 VIII 65 VIII)
 - (1) Etiology—due to a selective deficiency of gonadotropins and normal secretion of other pituitary hormones
 - (2) Synonyms
 - (a) Primary pituitary gonadotropic failure
 - (b) Secondary hypogonadism or hypopituitarism
 - (c) FSH negative eunuchoidism
 - (3) Height age—normal
 - (4) Bone age—retarded
 - (5) Growth rate—normal
 - (6) Span—increased
 - (7) Breast development—absent

- (8) Testes
 - (a) Up to the age of 12 or 13 years may be
 - [1] Normal
 - [2] Small
 - (b) After 12 to 13 years—no further enlargement
- (9) Amenorrhea
- (10) Urinary FSH
 - (a) Decreased
 - (b) Absent
- (11) 17 ketosteroids—low for age

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A FROM INTRACRANIAL PRESSURE

- 1 Visual field defects
 - a Variable
 - b Blindness
- 2 Headache
- 3 Mental aberrations
- 4 Coma
- 5 Epilepsy

II FROM HORMONAL DEFICIENCIES

- 1 Stopped epiphyses
- 2 Unerupted teeth
- 3 Lethargy
- 4 Somnolence
- 5 Diabetes insipidus occasionally^{1 2 3 4 5 6 7}
- 6 Constipation

C RECURRENCE OF TUMOR—This depends on type

- 1 Craniopharyngioma may do so
- 2 Malignant growths often will (see Fig 23)

XVI TREATMENT

A HORMONAL

- 1 Thyroid (desiccated USP)^{6 10 34 35}
 - a Dosage
 - (1) Oral 1 to 2 gr daily
 - (2) Use with caution
 - b Results—may produce unexpected progress in some cases (see Fig 40 Protocol 3 IV Chart 16)
- 2 Chorionic gonadotropin (for males)^{1 2 3 4 5 6 7 8 9} (see Fig 30, Charts 14 and 15)
 - a Indication—patients who are 12 years of age or more
 - b Dosage—intramuscular—1 000 to 5 000 iu weekly
 - c Results
 - (1) Effect on growth is possible

- (2) Genital development
 - (3) Other secondary sex characteristics progress
 - (4) Fairly well tolerated and may be continued intermittently
- 3 Testosterone (for males)⁸⁹
- a Indications
 - (1) Promotion of
 - (a) Growth
 - (b) Muscular development
 - (2) To improve anemia
 - b Dosage
 - (1) Oral or buccal—methyltestosterone 20 to 30 mg daily
 - (2) Intramuscular—testosterone propionate, 50 to 70 mg weekly
 - (3) Pellets—testosterone, 150 mg average, implantation every 3 to 5 months
 - c Comment
 - (1) Before the age of 12 testosterone can be used without fear of premature epiphyseal closure
 - (2) Trial of chorionic gonadotropin for 2 or 3 months may be attempted before testosterone
 - (3) 'Lost growth' cannot be recovered
 - (a) Individual remains subnormal in stature
 - (b) One report of dwarf becoming giant⁶¹
 - d Result—growth spurt may not be maintained (see Figs 30 32 34 and 36)
- 4 Estrogens (for females)
- a Indications—to
 - (1) Develop secondary sex characteristics
 - (2) Stimulate growth (doubtful)
 - (3) Establish menstrual flow
 - b Dosage oral
 - (1) Stilbestrol—0.3 to 1 mg daily (if tolerated)
 - (2) Estrone sulfate—0.3 to 1.2 mg daily
 - (3) Other estrogens in comparative dosage progesterone may be used in conjunction with estrogens (see 65 XVI II E)
 - c Results
 - (1) Periodic flowing if medication is
 - (a) Continued until vaginal bleeding occurs
 - (b) Stopped when flow is present
 - (c) Resumed when menses cease
 - (2) Breast development progresses
 - (3) Hair growth is slight some functioning pituitary tissue is needed for adequate response
- 5 Desoxycorticosterone acetate (DOCA)
- a Indication—adrenal insufficiency of clinical significance rarely occurs but is possible (see 40 VIII)⁴⁹
 - b Dosage pellet—75 mg
 - c Results
 - (1) Well being improves
 - (2) Blood pressure rises
 - (3) Tolerance for desiccated thyroid may increase when testosterone is also administered
- 6 Adrenocorticotropin (see 106 III E)
- a Indications
 - (1) Same as for desoxycorticosterone
 - (2) Anorexia
 - b Dosage intramuscular—10 mg daily
 - c Results—should be favorable, based on adult studies
 - d Addition of testosterone is probably advisable in males
- 7 Growth hormone or anterior pituitary extracts have not yielded very satisfactory results to date^{73 74 77 84 86}
- 8 Combinations
- a Growth hormone with desiccated thyroid
 - (1) Dosage intramuscular
 - (a) Growth hormone—1 to 3 cc 5 to 7 times a week
 - (b) Chorionic gonadotropin—1 000 to 2 000 units 3 times a week
 - (2) Results—variable
 - b Testosterone and estrogen therapy in the female
 - (1) Indication—greater growth stimulus than with estrogens alone
 - (2) Dosage as above
 - (3) Results
 - (a) Estrogen may offset masculinizing effects

(b) Growth stimulus may not be maintained

c Adrenocorticotropin and testosterone for males (see above)

9 Cortisone—see 5 VII B 5

II INTRACRANIAL SURGERY^{10 14 15}

1 Indications for operation

a Intracranial pressure with or without localization of tumor if the following are present

(1) Headache, severe

(2) Visual damage

(3) Optic edema

b Large tumors not believed to be radiosensitive

2 Hormonal changes alone are not sufficient criteria for immediate surgery

3 Unnecessary risks should not be taken in any case

4 Air studies

a All cases where tumor is suspected to identify its

(1) Location

(2) Type

b Since chromophobe tumors are rare under the age of 15 it is advisable to establish nature of tumor before considering roentgen therapy; cranio-pharyngiomas are not very radio sensitive

5 Procedure—see 13 VII A

6 Results—see 12 IV

C ROENTGEN¹⁶

1 Indications

a Chromophobe tumor

b Prophylaxis against return of chromophobe or malignant tumor after operation

2 Procedure—see 13 IX A

3 Results depend on (see Fig 34)

a Radiosensitivity

b Degree of malignancy

XVII PROGNOSIS

A HEIGHT

1 Amount lost during retardation of growth may not be regained

2 Maximum to be hoped for is a normal rate of growth by

a Removal of tumor

b Medical treatment

3 Resumption of growth may take place spontaneously at any age (see Chart 13)

II SEXUAL DEVELOPMENT

1 This does not follow

a Surgery

b Roentgen radiation

2 Spontaneous recovery is possible (see Protocol 3 IV)^{17 18}

3 Pregnancy and newborn may be normal^{19 21 22 23}

4 Hormonal therapy

a Testosterone is helpful in males but spermatogenesis is unlikely

b Estrogens are useful in females

c Chorionic gonadotropin alone or with pituitary gonadotropins may be tried especially in males

XVIII CAUSES OF DEATH

A COMPLICATIONS^{24 25 26 27}

1 Tumor

2 Postoperative

B PNEUMONIA^{28 29}

C CACHEXIA (see Figs 43 and 44)

D TUBERCULOSIS^{31 32 33}

PREPUBERAL HYPOPITUITARISM

Family history Negative

Past medical Negative

Chief complaint Dizziness of 5 weeks duration

History of present illness Patient had dizzy spells noises in her head which were similar to buzzing sounds and diplopia No history of head injury impairment of speech, or loss of taste and smell Headaches not localized

PROTOCOL I FIG 29 CHART 13

1 Physical examination Age 14 years Female

Weight 72½ lbs Height 54 in BP 102/70

A well proportioned dwarfed child without

sexual development Axillary and pubic hair

absent Visual fields bitemporal hemianopia

with marked restriction Visual acuity

right 20/70 left 20/50 Heart and lungs

normal Neurologic examination normal

Laboratory data Urine normal RBC 4 000

000 Hgb 75% WBC 9,600 Differential

polymorphonuclears 56% lymphocytes 31%, monocytes 6% eosinophils 2%
Spinal fluid normal

Röntgenographic findings: Sella measures 14 mm in A-P and 8 mm in depth lateral area approximately 100 sq mm Posterior clinoids are upright in position and slightly thinned, calcification in midline just above the sella Total area of calcification measures more than 2 cm in diameter Chest normal

Treatment: Operation—large suprasellar craniopharyngioma was found and removed

Progress

MONTHS

14 Growth resumed No sexual development Mild diabetes insipidus RBC 4,640,000 Hgb 15.1 Gm WBC 8,000 Differential polymorphonuclears 44%, lymphocytes 46% monocytes 5% eosinophils 5% Plasma cholesterol 124 and 179 mg % Serum phosphorus 4.0 mg % Adrenal water test positive Urinary hormones FSH negative, estrin grade one 17 ketosteroids 2.5 mg/24 hrs

20 Stilbestrol ointment rubbed into axillae and pubis No hair growth

YEARS

3 Anterior pituitarylike hormone 1 cc (1,000 units) 3 times a week for 3

months without effect Stilbestrol, 0.5 mg orally daily

4 Stilbestrol 0.5 mg orally, tid and thyroid 1 gr daily for 18 months Occasional menstrual flow Oreton "M" ointment rubbed into axillae for several months No hair growth

6 Weight 138 lbs Final height 64½ in Feels perfect Normal intake of water No pubic or axillary hair Breasts enlarged and deeply pigmented Thyroid 1 gr daily

Comment: This case illustrates the usual history of a patient with craniopharyngioma namely retarded growth about which nothing was done, and cerebral symptoms for which medical advice was sought Operation was successful with resumption of normal growth rate but no further sexual changes were noted Mild diabetes insipidus developed postoperatively, and disappeared in several years Low 17 ketosteroids were found and a positive water test for adrenal cortical insufficiency In spite of latter, general strength and activity were normal No response to chorionic gonadotropin Stilbestrol caused enlargement of breasts and menstrual bleeding Growth rate apparently slowed down on this medication No growth of pubic or axillary hair with stilbestrol or axillary hair by local injection of testosterone ointment

JREPUERAL HYPOPITUITARISM—GROWTH AND GONADOTROPIC DEFICIENCY

PROTOCOL II FIG 30

Family history: Father 65 in 150 lbs Mother 66 in 103 lbs Sister age 15, 65 in, 101 lbs
Past medical: Pneumonia

Chief complaint: Failure to grow

History of present illness: Underweight since 8 years old but gained slowly for past 2 years At age 15 50 in and 84 lbs Grew 8 in from 11 to 17 years Mental development normal, a junior in high school

Physical examination: Age 17 male single Weight 90 lbs Height 54 in BP 104/96 Small for his age but well proportioned Short fat arms and legs Small hands and feet Skin smooth Fundi normal Thyroid not palpable Breasts prominent Fat belt around lower portion of abdomen Genitalia proportionate to height age

Laboratory data: Urine normal RBC 504,000 Hgb 92% WBC 7,450 Differential polymorphonuclears 55% lymphocytes 34%, monocytes 6%, eosinophils 4%, basophils 1% Plasma cholesterol 117 mg %

Röntgenographic findings: Skull—posterior clinoids directed posteriorly No other signs of intracranial lesion Dental age 13 to 14 years Bone age 12¼ years

Treatment and progress

MONTHS

10 Thyroid (desiccated USP) 1 gr daily and gradually increased to 2 gr Grew a little No sexual hair Plasma cholesterol 153 mg %

MONTHS

- 18 Growing slowly Testes firm, small olive size Urinary ISH negative un concentrated 17 ketosteroids 2.08 mg / 24 hrs Bone age 13½ years Thyroid, 2 gr daily to be continued
- 33 Further growth Erections at times Testes larger Plasma cholesterol 136 mg % Urinary ISH negative 17 ketosteroids 3.0 mg / 24 hrs (880 cc volume)
- 44 Weight 120 lbs Grew 1½ in in past 12 months Testicles larger No sexual hair Methyltestosterone, 10 mg b i d to t i d
- 47 Height 59 in Noted no effect from testosterone, so stopped taking it Chorionic gonadotropin (APL) 1 cc (1 000 units) injections 3 times a week
- 49 Pubic hair and axillary hair appeared while on APL injections
- 54 Gained 19 lbs Grew 1¾ in with APL injections Height 60¾ in Genitalia larger Approximate volume of each testis 13 to 18 cc Bone age 15¼ yrs
- 66 Weight 135 lbs Height 61¼ in No medication for 9 months Penile erec

tions No facial hair Testes same size Serum phosphorus (fasting) 4.8 mg %

- 76 Weight 141 lbs Height 61½ in No medication for 10 months Grew only ¾ in, but bone age at stage when growth rate declines Serum phosphorus 4.7 mg %

Comment Dwarfism of pituitary origin illustrating retardation of growth and sexual development but otherwise a well and active patient Suprasellar cyst suspected but never proved Hypogenitalism was related only to chronologic age, but not to height or somatic age The marked discrepancy between bone and chronologic ages is characteristic of pituitary dwarfism in contrast with simple delayed puberty Continued increment of growth with some response to methyltestosterone and further development with chorionic gonadotropin On cessation of chorionic gonadotropin and testosterone there was less progress Inorganic serum phosphorus levels suggest independent growth hormone activity Although 25 years of age sexual maturity may still occur

PREPUBERAL HYPOPITUITARISM

PROTOCOL III

FIGS 36, 37

CHARTS 14 15

Family history Negative

Past medical Negative

Chief complaint Failure to grow normally about 2 years

History of present illness From 3 to 6 years before admission it became apparent to his parents that the patient was not growing as other children His brother 2 years younger was one head taller Intelligence average junior in high school

Physical examination Age 14 male single Weight 61 lbs Height 49 in Pulse 80 BP 95/70 A small well proportioned boy with physical characteristics of an 8 year old Pubic and axillary hair absent Breasts normal Penis and testes very small

Laboratory data Urine normal Plasma cholesterol 229 mg %

Roentgenographic findings Skull—ella normal definite widening of the coronal and sagittal sutures for his age possible in

creased intracranial pressure Dental age 12 or 13 years Bone age 7 to 8 years

Treatment and progress

YEAR

- 1 Growing very slowly RBC 4 080 000 Hgb 77% WBC 6 150 Differential polymorphonuclears 47% lymphocytes 35% monocytes 6% eosinophils 10.5% basophils 1.5% Plasma cholesterol 316 mg % Skull—sutures lines remain open but are not separated sella normal
- 2 Growing very slowly Thyroid (desiccated USP) ¼ gr daily restarted and continued for 1 year
- 5 Thyroid medication stopped
- 7 Growth very slow Absent sexual development and beard Feels perfectly well Blood counts the same Blood sugar 110 mg % (1½ hrs p c) Plasma cholesterol 253 mg % BMR

- minus 18% Skull sutures remain open Dental age 13 years Epiphyseal status (bone age) 13 years approximately Testosterone in glycolalcohol, 6 mg daily sublingually Thyroid 2 gr daily
- 8 Slight increase in pubic hair and a few penile erections Plasma cholesterol, 223 306 and 250 mg % Urinary FSH negative (unconcentrated) 17 ketosteroids 91 mg/24 hrs Bone age 15 years Methyltestosterone 20 mg daily for 2 months Seven testosterone pellets were implanted 3 on one occasion, 4 on the next
 - 9 Slight moustache more hair around the pubic area Few erections Voice lower Further secondary sex changes Testes not enlarging Plasma cholesterol 133, 178 and 254 mg % Urinary FSH positive 17 ketosteroids, 68 mg/24 hrs (volume 520 cc) Bone age 16¼ years Desiccated thyroid used intermittently to determine its effect on growth Testosterone pellets were inserted 4 times total of 18
 - 10 Fewer erections than before Voice unchanged No growth on thyroid and/or
 - 11 testosterone Plasma cholesterol 217 and 248 mg % Serum phosphorus 3.6 mg % Urinary hormones FSH nega-

tive, estrin negative, 17 ketosteroids 56 mg/24 hrs (volume 1,500 cc) Thyroid was taken irregularly Testosterone pellets, total of 8 during 9 months More erections Testicles no larger Semen volume 5 cc, sperm have no heads and are inactive Sella measures 68 sq mm Bone age 17 years Four testosterone pellets

- 12 General condition about the same No complaints Above average intelligence Testicular volume about 5 cc each Chorionic gonadotropin, 3 000 to 5 000 units per week, for 7 months without testosterone Erections maintained Adrenal water test negative

Comment Pituitary dwarfism which responded to testosterone therapy Although patient always felt well, there was apparently some secondary thyroid deficiency Adrenal water test negative Urinary FSH negative twice and positive once 17 ketosteroids from 5 to 11 mg/24 hrs Increased erections and nocturnal emissions on chorionic gonadotropin but little or no increase in testicular size, showing that Leydig cells reacted but tubules did not and no spermatozoa were seen in ejaculate The cause of tubular failure might be assigned to long absence of stimulation independent disease of tubules or too much testosterone

PITUITARY DWARFISM

Family history Grandmother and mother each about 4 ft 10 in in height Father was 5 ft 7 in Two brothers were of normal height

Past medical At birth weighed 7 to 8 lbs therefore normal in size although no measurement of length recorded He seemed to develop normally until about 4 yrs of age when he stopped growing At 8 yrs of age he was a patient at the Peter Bent Brigham Hospital Weight 28 lbs Height 35½ in Physical examination was summarized there as follows Proportional infantile boy, skin dry pale a few more wrinkles on the face than usual and little subcutaneous fat Mentality advanced Skull negative Delayed dental development Diagnosis Simmonds disease Bone age 2.9 years "

PROTOCOL IV FIGS 40-42 CHART 16

Chief complaint Failure to grow

History of present illness Patient has been normal except for his stature He has grown about 2 in a year since age of 10

Physical examination Age 15 male, single Weight 41 lbs Height 40¼ in Span 38½ in Pulse 76 BP 108/70 Alert mentally (in second year of high school) Proportionate infantile boy Hair fine normal amounts Genitalia flat pad over pubis penis and testes undersized

Laboratory data Urine normal RBC 4 300, 000 Hgb 78% WBC 10 800 NPN 24 mg % Plasma cholesterol 280 mg % BMR minus 18%

Röntgenographic findings Skull normal with very few convolutional markings Epiphyseal status (bone age) 4½ years Chest normal

Treatment and progress (see growth chart)
MONTHS

- Thyroid (desiccated USP) $\frac{1}{2}$ gr daily because of cholesterol and metabolic rate
- 2 Grew 1/16 in on thyroid medication Appetite improved
- 3 Thyroid dose increased to 1 gr Grew $\frac{1}{2}$ in Two deciduous teeth appeared
- 7 Patient growing No weight gain Bone age 6 years Thyroid 1 gr daily continued halibut oil 1 capsule daily 1 year vitamin B syrup (Meads) 2 teaspoonfuls daily 6 months
- 19 Bone age 10 years Patient was sent to Irrelaban for injections Unfortunately he already began to show pubic hair so that the pituitary preparation had no relationship to the onset of puberty (between 17 and 18 years of age) No growth spurt noted as result of injections
- 26 Bone age 12 to 14 years Thyroid 2 gr daily
- 34 Three gr of thyroid for 2 months then no further treatment
- 36 Bone age 15 $\frac{1}{4}$ years
- 55 Patient was not seen since the thirty-sixth month of treatment Plasma cholesterol (note on chart) which had been elevated at the onset and had de-

creased with thyroid administration, was lower than while taking it 2 years previously Radial epiphyses closed

- 57 Measurement from the umbilicus to floor was 28 $\frac{1}{2}$ in Weight 70 lbs Proportionate development for height age Facial lanugo was present Testes normal for patient's size Prostate was small RBC 4 890 000 Hgb 99% Sperm count 104 000 000/cc, 80% motile majority were normal few with large round heads short thick necks and some miniature forms EKG normal 17 ketosteroids 3.3 mg/24 hrs (volume 200 cc) Chest and skull normal Thyroid (desiccated, USP) 1 gr started for 2 weeks then increased to 2 gr daily
- 63 Axillary hair present and facial hair had increased Voice changing Normal sexual drive Height remained 50 in Good health 17 ketosteroids 10 mg/24 hrs (volume 650 cc) Urinary FSH negative (unconcentrated)

Comment Dwarfism of pituitary origin affecting only growth and possibly thyrotropic hormone Desiccated thyroid appeared to stimulate growth and normal sexual development between 17 and 18 years Final height 50 in

REFERENCES

- 1 Altmann F Hypophysärer Zwergwuchs bei einem weiblichen Individuum Beitr z path Anat u z allg Path 85 205 220 (July) 1930
- Apitz K Zur Pathogenese des hypophysären Kleinwuchses Arch f path Anat 302 553 579 1938
- 3 Babinski M J Tumeur du corps pituitaire sans acromégalie et avec arrêt de développement des organes génitaux Rev neurol 8 531 533 (June) 1900
- 4 Baker A and Craft C Bilateral localized lesions in the hypothalamus with complete destruction of the neurohypophysis in a pituitary dwarf with severe permanent diabetes insipidus Endocrinology 26 801 806 (May) 1940
- 5 Bartels M Ueber die Beziehungen von Veränderungen der Hypophysengegend zur Misswachsung und Genitalstörungen (Dystrophia adiposa genitalis) München med Wchnschr 4 201 (Jan) 1903
- 6 Bayer L M and Gray H Pituitary dwarfs their growth and treatment California & West Med 47 228 233 (Oct) 1937
- 7 Beck H and Suter G M Pituitary dwarfism with diabetes mellitus Endocrinology 22 115 119 (Jan) 1938
- 8 Beckmann J W and Kubie L ■ A clinical study of 21 cases of tumor of the hypophyseal stalk Brain 32 127 169 (July) 1919
- 9 Benda C Beiträge zur normalen und pathologischen Histologie der menschlichen Hypophyse des cerebr. Klin Wchnschr 37 120, 1210 (Dec) 1900
- 10 Bennett L L Weinberger H Escamilla R Margen ■ L C H and Evans H M Failure of growth hormone to produce nitrogen storage in hypophyseal dwarf J Clin Endocrinol 10 492 495 (May) 1950
- 11 Bethlinger W Zur Kenntnis des pituitären Kleinwuchses Beitr Path Anat u allg Path 87 233 256 1931
- 12 Bronstein I P and Cassoria E Pituitary dwarfism? Spontaneous correction J Pediat 28 618 620 (May) 1946
- 13 Bronstein I P and Fabricant N D Pituitary dwarfism with atrophic rhinitis Am J Dis Child 60 1140 1146 (Nov) 1940

- 14 Buchanan J A and Ballweg H A case of pituitary dwarfism treated with Antutrin *Endocrinology* 24 565 571 (Apr) 1939
- 15 Burton St J D Pituitary cyst with dwarfism and delayed union of fracture *Brit J Surg* 27 181 183 (July) 1939
- 16 Cohen M M and Wagner R Dental development in pituitary dwarfism *J Dent Res* 27 445 458 (Aug) 1948
- 17 Conley T M Adamantinoma of the cranio-pharyngeal duct occurrence in a child manifesting marked cachexia and dyspituitarism of the Lorain type *Am J Dis Child* 61 1275 1308 (June) 1941
- 18 Cushing H Pituitary Body and Its Disorders Philadelphia pp 59 66 87 Lippincott 1912
- 19 *ibid* pp 42 84
- 20 — The intracranial tumors of preadolescence *Am J Dis Child* 33 551 554 (Apr) 1927
- 21 — Neurohypophyseal mechanisms from clinical standpoint (Lister memorial lecture) *Lancet* 2 119 (July) 1930
- 22 Daughaday W H Jaffe H and Williams R W Chemical assay of urine for adrenocortical hormones in endocrine and non endocrine diseases pp 18 19 Assn Study Int Secretions Program 29th Meeting Atlantic City N J June 6 7 1947
- 23 Dorff G B Case of pituitary infantilism treated with commercial anterior pituitary preparations *Endocrinology* 19 209 212 (Mar-Apr) 1935
- 24 — Gonadotrophins and linear growth *Am J Dis Child* 64 661 673 (Oct) 1942
- 25 Dott N M Bailey P and Cushing H Hypophysial adenomata *Brit J Surg* 13 314 316 (Oct) 1925
- 26 Engelbach W Growth hormone report of case of juvenile hypopituitarism treated with Evans growth hormone *Endocrinology* 16 1 19 (Jan Feb) 1932
- 27 Engelbach W Schaefer R L and Brosius W L Endocrine growth deficiencies diagnosis and treatment *Endocrinology* 17 250 262 (May June) 1933
- 28 Erdheim J Namosomia pituitaria *Beitr z path Anat u z allg Path* 62 307 377 1916
- 29 Falta W Endocrine Diseases ed 3 ■ 324 Philadelphia Blakiston 1923
- 30 Faneau de la Cour F V Du féminisme et de l'infantilisme chez les tuberculeux No 1 p 1 Paris Accouchements—Faculté de Médecine de Paris 1871
- 31 Faurbye A Pituitary dwarf *Acta psychiat et neurol* 21 245 256 1946
- 32 Foerster O Gagel O and Mahoney W Vegetative Regulationen Verhandl d deutsch Gesellsch f inn Med Kong 49 pp 165 187 1937
- 33 Frazier C H and Alpers B J Adamantinoma of the craniopharyngeal duct *Arch Neurol & Psychiat* 26 905 965 (Nov) 1931
- 34 Fraser R W Forbes A P Albright F Sul kowitch H and Reimenstein E C Jr Colorimetric assay of 17 ketosteroids in urine survey of use of this test in endocrine investigation diagnosis and therapy *J Clin Endocrinol* 1 234 256 (Mar) 1941
- 35 Frohlich A Ein fall von tumor der Hypophysis cerebri ohne akromegalie *Wien klin Rundsch* 15 883 886 15 906 908 1901
- 36 Gjurup E Hypophyseal nanism resulting from craniopharyngeoma *Acta paediat* 27 508 516 1940
- 37 Goldberg M M Treatment of pituitary in infantilism with antutrin report of case *Endocrinology* 18 235 234 (Mar-Apr) 1934
- 38 — Treatment of pituitary infantilism with anterior pituitary extract *Endocrinology* 20 854 855 (Nov) 1936
- 39 Goldstein K Kasuistische Mitteilungen zur Klinik und pathologischen Anatomie der Nervenkrankheiten *Deutsche Ztschr f Nerven* 103 225 274 (May) 1928
- 40 Gordon M B and Kuskin L Endocrine studies in infants and children time of onset of teething walking and talking in endocrine disorders its relationship to intelligence in endocrine and nonendocrine conditions *J Pediat* 7 ■ 98 (July) 1935
- 41 Greene J A and Johnston W Metabolic changes by extracts of anterior hypophysis in primary pituitary and in nonpituitary dwarfism *J Clin Endocrinol* 1 327 330 (Apr) 1941
- 42 Hare H F Personal communication
- 43 Heinrichs H Zur Frage der Dystrophia adiposa genitalis *Frankfurt Ztschr f Path* 41 512 520 1931
- 44 Hewer T F Ateleiotic dwarfism with normal sexual function a result of hypopituitarism *J Endocrinol* 3 397 400 (May) 1944
- 45 Holmes G Pituitary disorders *Brit M J* 2 1035 1040 (Dec) 1926
- 46 Horrat G H Personal communication
- 47 Huesser J Ein Beitrag zur Kasuistik der Hypophysistumoren *Virchows Arch f path Anat* 110 9 20 1887
- 48 Hueter C Hypophysis tuberkulose bei einem Zwergling *Virchows Arch f path Anat* 187 210 236 1905
- 49 Hurthall L M Unpublished data
- 50 — Proportional dwarfism with delayed sexual maturity apparent response to desiccated thyroid *Lahey Clin Bull* 4 186 192 (Oct) 1945
- 51 Jores A Hypophysärer Zwergwuchs *Klinische Endokrinologie* 7 Ausg p 71 Berlin 1942
- 52 Kon J Seltene Perithelom teleangiectatisches Sarkoma *Beitr z path Anat u z allg Path* 44 233 266 1908
- 53 Laha P N Frohlich's syndrome (with 2 illustrative case reports) *Antiseptic* 42 236 242 (May) 1945
- 54 Lauros P E and Clérét M Le syndrome hypophysaire adipo-genital *Gazette Heb* 83 57 64 (Jan) 1910
- 55 Lawrence C H and Harrison A Pituitary dwarfism case report illustrating response to treatment *Endocrinology* 23 360 363 (Sept) 1938
- 56 Leschke E Clinical pathology of midbrain *Deutsche med Wchnschr* 46 959 (Aug) and 996 (Sept) 1920
- 57 Levi E Contributions à l'étude de l'infantilisme du type Lorain *Nouv Icon de la Salpêtr* 21 297 421 1908
- 58 Looney J M Treatment of pituitary dwarfism with growth hormone *Endocrinology* 26 163 166 (Jan) 1940
- 59 Love J G and Marshall T M Cranio-pharyngiomas (pituitary adamantinomas) *Surg Gynec & Obst* 90 591 601 (May) 1950
- 60 Luft W Chronic gonadotrophins in treatment of disturbances of development in childhood

- and adolescence *Acta paediat* 33 211 229 1946
- 61 Mandl A. and Windholz Studies on a case of gigantism following arrest of growth *Zeitsch f die ges Neurol u Psychia* 137 649 68 1931
- 62 Maranon G Pituitary obesity *Deutsches Arch klin Med* 151 129 153 (May) 1926
- 63 Mason J T and Turner H C Cesarean section on dwarf aged 40 years *B Clin North America* 8 1453 1455 (Dec) 1928
- 64 McCullagh E P., and Kline I T Absence of pituitary failure in fat boys with testicular deficiency *Cleveland Clin Quart* 13 10 18 (Jan) 1946
- 65 Mehenze A G and Sosman M C The roentgenological diagnosis of craniopharyngeal pouch tumors *Am J Roentgenol* 11 171 176 (Feb) 1924
- 66 Morgenstern Dystrophia adiposo genitalis Virchow's Arch f path Anat 239 557 567 1922
- 67 Donne M Nachtrag weiterer erwachsener Kasuistik seit Anfang 1914 *Deutsche Ztschr Nervenh* 55 29 47 (Sept) 1916
- 68 Paschke K E Hypophysis in protein metabolism is pituitary factor active in protein metabolism identical with growth hormone? *Endocrinology* 23 368 370 (Sept) 1938
- 69 Faulkner V Der Zwergwuchs in gerichtlicher und anatomischer Beziehung Wien 1891
- 70 Priesel A Ein Beitrag zur Kenntnis des hypophysären Zwergwuchses *Beitr path Anat u allg Path* 67 2 274 1920
- 71 Rolleston H D The Endocrine Organs in Health & Disease 127 New York Oxford University Press 1936
- 72 Rowe A M Endocrine studies the gaseous metabolism of some dwarfs and giants *J Nutrition* 7 573 590 (June) 1934
- 73 Schaefer R L Endocrine dwarfism growth *Endocrinology* 20 64 71 (Jan) 1936
- 74 Schaefer R L and Strickroot F L Endocrine dwarfism *Endocrinology* 26 599 604 (Apr) 1940
- 75 Schumacher J Dystrophia adiposo genitalis nach Schadeltrauma *Deutsche med Wchnschr* 63 1648 1651 (Oct) 1937
- 76 Schwartz K Der hypophysäre Zwergwuchs im Kind salter Ergebn d inn Med u Kinderh 58 285 330 1940
- 77 Shelton F K The clinical aspects of dwarfing *Endocrinology* 30 1000 1014 (June) 1942
- 78 Shelton F K, Cavanaugh L A and Evans H M Hypophysial infantilism treatment with anterior hypophysial extract preliminary study *Am J Dis Child* 47 719 736 (Apr) 1934
- 79 Simmonds M Zwergwuchs bei Atrophie des Hypophysenorderlappens *Deutsche med Wchnschr* 45 487 (May) 1919
- 80 Speck G Pregnancy in cases of pituitary dwarfism *Am J Obst & Gynec* 51 217 220 (Feb) 1946
- 81 Stephens D J Hypopituitarism *Internat Clin* 1 97 109 (Mar) 1939
- 82 Stumpf Untersuchungen über das Verhalten des Hirnanhangs bei chronischem Hydrocephalus und über den Ursprung der Ferment granulationen in der Neurohypophyse *Virchow's Arch f path Anat* 209 339 352 1912
- 83 Taylor N M Pituitary dwarfism treatment with growth hormone *Endocrinology* 22 57 71 (June) 1938
- 84 Turner H H Anterior pituitary dwarfism further report of cases treated with growth hormone *South Med J* 28 309 316 (Apr) 1935
- 85 Vazourou A and Delmas A Infantisme et insuffisance dia tématique *Nouv Icon de la Salpet* 20 338 247 1907
- 86 Wang C C, Hogden C., Kaucher M and Wing M Metabolic study of case of Loran type of infantilism *J Biol Chem* 100 99 100 (May) 1933
- 87 Weber F P Atelosis *Brit J Child Dis* 13 200 (July) 1916
- 88 Wilkins L Conference on Metabolic Aspects of Convalescence including Bone and Wound Healing 4th Meeting June 11 12 New York Josiah Macy Jr Foundation 1943 pp 141 150



FIG 27 FROHLICH'S SYNDROME Illustrating that retardation of growth and sexual development and not obesity are the important physical findings in this disorder. Age 14 estimated height 46 to 48 in. Height age 7 to 8 years. Although obesity is reported to have occurred in this patient at a later date it is now considered to have resulted from hypothalamic injury rather than anterior pituitary hypofunction. The patient suffered from headaches and visual changes due to a suprasellar cyst (Frohlich A. Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie. Wien klin Rundschau 15: 883).

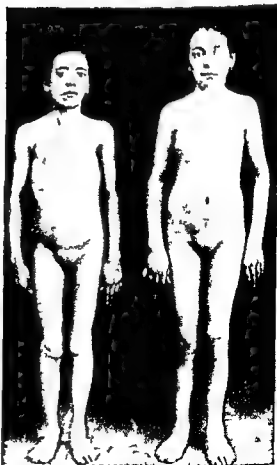


FIG 28 LORAIN LEVI TYPE OF INFANTILISM This disorder is the same as Frohlich's syndrome. The two sisters shown here were 15½ and 20 years of age. In one an enlarged sella was demonstrated along with visual changes; no such abnormality was found in the other. Both were dwarfed (51 and 52 in. height age 9 to 10 years) and had no sexual development (Faneau de la Cour, a student working with Lorain, first published a description of infantilism associated with pulmonary tuberculosis; hence the reason for the term Lorain Levi Gynecomastia as well as eunuchoidism without dwarfism was also described in the same article. Faneau de la Cour. Du féminisme et de l'infantilisme chez les tuberculeux. Jan. 1871. Faculté de Médecine). (Reproduction of illustrations from original article. Levi E. Contributions à l'étude de l'infantilisme du type Lorain. Nouv icon de la Salpêtr 21: 297).

FIG 29 PANHYPOPHYLLITISM CAUSED BY A SUPRASELLAR CYST (See Protocol 3 I Chart 13) Age 14 Height 58 in Height age 12 to 13 years Span 57½ in Bone age 12½ years BMR plus 7% Patient shows retarded growth and sexual development due to craniopharyngioma These abnormalities were not considered important by her parents until she complained of double vision and dizziness associated with head noises Mentally precocious Resumption of normal rate of growth after craniotomy but no sexual development or re growth of body lanugo Mild diabetes in ipidus since operation

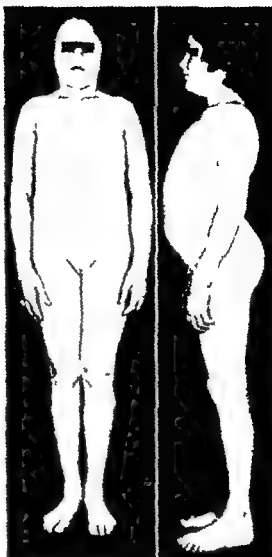
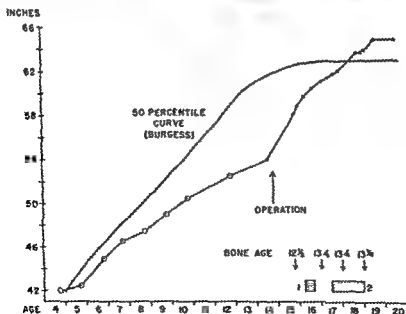


CHART 13 PANHYPOPHYLLITISM (See Fig 29) Growth chart before and after operation for craniopharyngioma Note that growth has continued into the nineteenth year having been retarded since the age of 8 and accelerated after operation (1) Stilbestrol injection in left axilla (0.5 mg daily) was without effect Treatment with chorionic hormone and pregnant mare serum was unsuccessful (2) Stilbestrol (0.5 to 1.5 mg daily) administration beginning at the age of 19 produced menstruation and slight enlargement of breasts without pubic or axillary hair growth Linear growth slowed down with this treatment Injections of testosterone in axillae failed to cause hair growth there



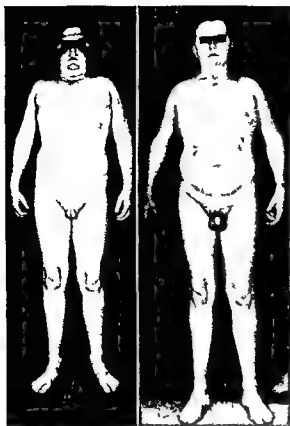


FIG 30 PITUITARY DWARF (See Protocol 3 II) (Left) Age 17 Height 54 in Height age 10½ years Bone age 11 years Gradual growth for 3 years not accelerated by treatment with desiccated thyroid Genitalia not disproportionately small for height age Testicular volume estimated 4 cc (Right) Height 60¼ in (5 years later) Testicular volume 8.5 cc after 6 months of methyltestosterone (10 to 20 mg daily) No apparent increase in growth rate On chorionic hormone (1000 units 3 times a week) for the greater part of 9 months patient grew 1¾ in an increased growth rate Testicular volume estimated 13 to 18 cc Note condition of genitalia



FIG 31 CRANIOPHARYNGIOMA AND PANHYPOPITUITARISM (Right) Skull in an individual 25 years of age Note the large suprasellar cyst with calcification the underdevelopment of the sinuses the rather than cranial bones and the open sutures The result of craniotomy (by Dr Harvey Cushing) at the age of 16 is seen which probably permitted further growth but absence of secondary sex characteristics remained Weight 97 lbs RBC 4 600 000 Hgb 92% Plasma cholesterol 164 mg % Serum sodium 125.5 mEq/l Serum potassium 17.3 mg % Plasma chlorides 508 mg % Glucose tolerance test ½ hr 60 mg % 1 hr 100 mg % BMR minus 40% Bone age 15 years (Left) Hand of patient demonstrating open epiphyses which are slow but continual growth until age of 25 when he attained a height of 67½ in



FIG 32 HYPOPHYLLITARISM WITHOUT GROWTH RETARDATION (See Fig 33) Complaints pallor and weakness Age 19 Height 67 $\frac{1}{4}$ in taller than parents and 6 siblings Span 68 in Bone age 16 years No axillary pubic or body hair Testes approximate volume 5.5 cc (average for 14 year old) RBC 3 200 000 to 4 600 000 Hgb 72 to 86% and 83% after testosterone therapy Differential polymorphonuclears 55% lymphocytes 37% monocytes 3% eosinophils 2% and basophils 2% Plasma cholesterol 230 mg % Adrenal water test positive 1: ketosteroids 3.8 mg/24 hrs Sella enlarged and unusual in shape Visual fields normal No headaches Surgery and air studies not indicated No improvement on 20 units of gonadogen 3 times a week for 6 months other than a few erections for several months Testosterone by pellets or sublingually caused improvement in well being strength and endurance Pubic hair developed but fell out when treatment was omitted Height at 22 was 69 in span 72 in Bandage is over site of pellet implantation

FIG 33 HYPOPHYLLITARISM WITHOUT GROWTH RETARDATION (See Fig 32) Sella enlarged measuring 10 x 15 mm or 133 sq mm The cause of sellar enlargement in this case is obscure it does not appear like the usual intrasellar tumor and there is no increase in size over a 3 year period The patient differs from an individual with hypopituitarism from suprasellar cyst because there is no growth retardation A mixed pituitary tumor might produce this clinical syndrome



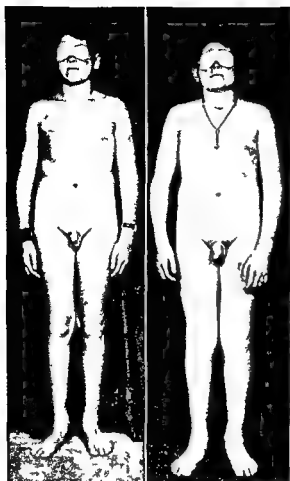


FIG 34 PINEALOMA SIMULATING CRANIOPHARYNGIOMA (See Fig 35) (Left) Photograph of patient shortly after operation. The tumor was malignant and was considered to be a pinealoma (Dr Louise Eisenhardt). Intensive irradiation after operation consisted of 4 000 r total to each of 3 portals. Patients complained of headache and had a bitemporal hemianopsia before operation. A mild diabetes insipidus was also present. He was 12 years of age and measured 56 1/2 in (normal for age). Bone age normal (12 years). (Right) After testosterone therapy. From time of operation age 12 little growth occurred. One year after operation when thyroid (desiccated USP) 2 gr was given a drop in weight followed but there was a consistent increase in growth. This apparently ceased when thyroid was discontinued and little effect was noted when it was resumed in a dose of 1 gr daily. There probably was a further stimulation of growth and weight on gonadotropic and chorionic hormones which continued after giving methyltestosterone and testosterone pellets. Testes increased approximately from 3 1/2 to 1 1/2 in long (volume 2 to 4.5 cc approximately).

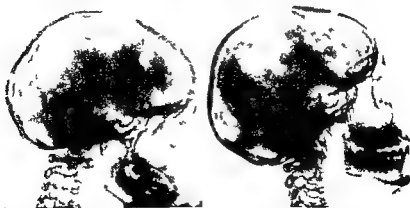


FIG 35 PINEALOMA SIMULATING CRANIOPHARYNGIOMA (See Fig 34) Roentgenograms after operation (Left) 6 months (Right) 18 months (essentially the same as before). Note recalcification of the posterior clinoids and smaller size of the sella a finding often seen after successful radiation therapy.

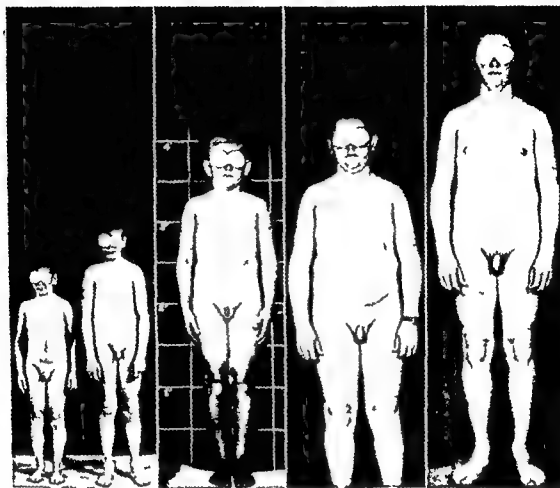


FIG 36 HYPOPITUITARISM (See Protocol 3 III Fig 37 Charts 14 and 15) (*Extreme left*) Pituitary dwarfism predominantly growth sex and thyroid deficiencies without evidence of pituitary tumor or cr. meningioma but with a small sella turcica Patient (*left*) age 14 and brother age 10 No complaints other than failure to grow for the previous 3 years Note amount and contour of pubic fat as compared with brother Mentally alert and normal intelligence Height 49 in Height age 8 years Bone age 7 years Weight 67 lbs RBC 4 000 000 Hgb 17% Plasma cholesterol 229 to 316 mg % BMR minus 18% (*Left of center*) Close up of subject at left (*Right of center*) Patient at age 21 Weight 132 lbs Height 59½ in Bone age 13 years RBC 4.1 million Hgb 76% Blood sugar 110 mg % (1½ hrs) Plasma cholesterol 253 mg % BMR minus 18% Treatment failed to produce any marked change in growth (*Extreme right*) End result of therapy demonstrated No acceleration of growth produced although epiphyseal closure took place Final height 63½ in Normal libido and ejaculation but aspermia Testes approximate volume 5.5 cc Patient takes methyltestosterone and desiccated thyroid Adrenal water test negative

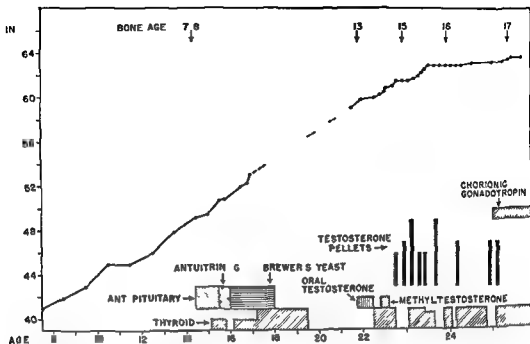


CHART 14 PITUITARY DWARFISM—GROWTH CHART (See Protocol 3 III Figs 36 37 Chart 15) No effect on rate of growth with various forms of treatment. At 8 years of age patient was underheight (below 1 percentile curve by Burgess). Treatment with anterior pituitary extract and thyroid (desiccated USP) ineffective. With growth hormone there appeared to be a spurt in growth and later with desiccated thyroid. This chart demonstrates the danger of making conclusions regarding the effects of any therapy over short periods of time. The dotted line represents a time span where no observations are made. See Chart 15 for effect of thyroid (desiccated USP) and testosterone on weight in this case.

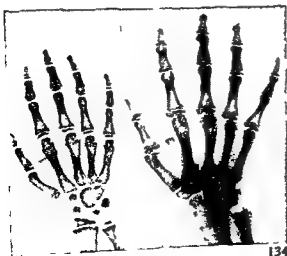


FIG 37 BONE MATURATION IN PITUITARY DWARFISM (See Protocol 3 III Fig 36 Charts 14 and 15) Bone age on admission and 1 years later (Left) Age 14 bone age 7 to 8 years (Right) Age 21 bone age 13 years

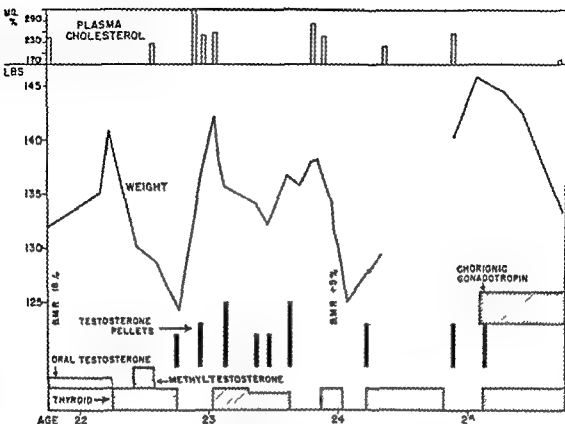


CHART 15 PITUITARY DWARFISM (See Protocol 3 III Figs 36 37 Chart 14) Effect of testosterone and thyroid (desiccated USP) on weight. Average growth rate before treatment was $1\frac{1}{2}$ in/year after treatment each year first $1\frac{1}{2}$ in second $1\frac{1}{4}$ in third $\frac{1}{2}$ in fourth no growth. Epiphyseal closure took place during last 2 years which accounted for slowing down in growth. No growth stimulation was accomplished with testosterone with or without thyroid (desiccated USP). The weight gain with testosterone is well shown and its tendency to prevent weight loss when thyroid (desiccated USP) is given. Chorionic hormone caused some increase in testicular size and also maintained the frequency of erections. However no spermatogenesis was evident after 6 months of chorionic hormonal therapy. The BMR was minus 18% without thyroid (desiccated USP) and the plasma cholesterol varied with 203 to 308 mg %. With thyroid (desiccated USP) the BMR was plus 5% and the plasma cholesterol was from 172 to 217 mg %.

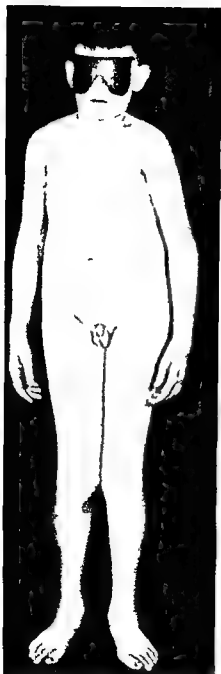


FIG 38 HYPOPITUITARISM (?)
Condition associated with central nervous system disease possibly due to birth injury. Mother had toxemia of pregnancy; child was delivered 2 months prematurely by internal podalic version and breech. Birth weight 4 lbs 9 oz. Mentally alert. Bilateral flexion contractures of both knees with muscular atrophy. Age 17.

Height 62 in. Height age 14 to 15 years. Bone age 14 years. BP 90/0. RBC 3,000,000. Hgb 11.5 Gm. Differential normal. Plasma cholesterol 188 mg %. BMR minus 20 %. Urinary FSH questionable weak positive. 17 ketosteroids 3.7 mg/24 hrs. Treated with methyltestosterone (40 mg daily) with resulting weight gain and genital development. Final outcome unknown.

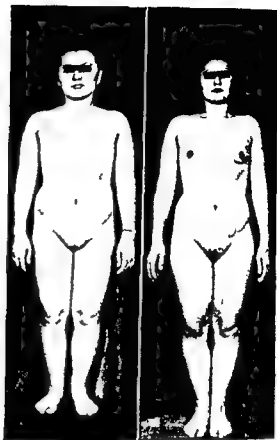


FIG 39 HYPOPITUITARY DWARF (Left) Age 17. Bone age 10 years. Height age 10 years (53 in). Serum phosphorus 3.8 mg %. Urinary FSH negative. Only complaint failure to menstruate. Unresponsive to chorionic hormone and pregnant mare serum. (Right) Age 21. Bone age 13½ years after 6 months of stilbestrol therapy (0.5 to 1 mg daily). Height age 11 years (55½ in). Periodic menstrual flow, enlargement of breasts and some growth of pubic and axillary hair. (Patient always had some hair on arms and legs). Urinary pregnandiol negative preceding menstrual flow. Compare with Figure 29 in which breast development and menstrual flow occurred without hair growth. At age 23 spontaneous menstruation occurred regularly without medication for 6 months.

FIG 40 PITUITARY DWARFISM (See Protocol 3 II Figs 41-42 Chart 16) Apparent response to treatment with desiccated thyroid. Epiphyses closed at 21 years. Normal sexual development with normal spermatogenesis. Final height 50 in. Height age $8\frac{1}{2}$ years.

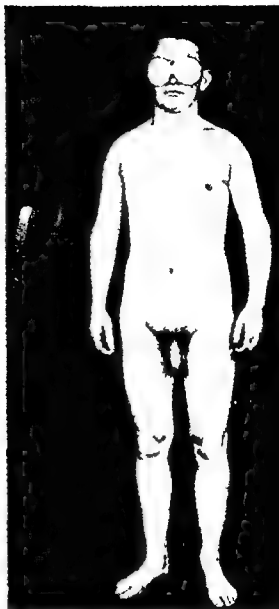


FIG 41 PITUITARY DWARFISM SELLAE ROENT GENOGRAMS (See Protocol 3 II Figs 40-42 Chart 16) (Left) Age 8. Dental age on roent genograms was not retarded. Sella measured 6 x 4 mm. and the lateral contour area 33.5 sq. mm. which is small for chronologic age as well as for height age of $4\frac{1}{2}$ years. (Right) Age 21. Dental age on roent genograms was not retarded. The change in the sella size was slight and is still small for his height age. Note shape of skull which is unlike that of cretins. Poor development of sinuses. Sutures are open.



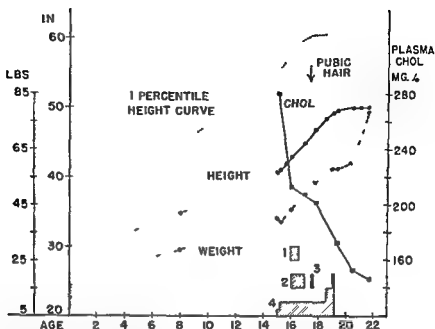


CHART 16 GROWTH CHART IN PITUITARY DWARFISM (See Protocol 3 IV Figs 40-42) The slow and verified rate of growth until the age of 15 is followed by an accelerated rate on administration of thyroid (desiccated USP). Note that growth slowed down when thyroid was discontinued but this was due to closing epiphyses. Thyroid was not stopped earlier because of his parents' desire not to interfere with the apparent effect of treatment. It is to be noted that the plasma cholesterol did not rise after omitting the medication. However, the patient continues to take 1 gr. of thyroid (desiccated USP) daily because he feels better and is less constipated. Without the drug the patient did not develop evidence of thyroid deficiency. Figure 40 shows him at that time. All the hollow and black circles represent recorded measurements. Plasma cholesterol is illustrated by black squares.

Key to therapy symbols in lower right section of chart: (1) Vitamin B complex 1 teaspoonful 3 times a day; (2) Haliver oil capsule 3 times a day; (3) Praeloban 100 mg twice a week; (4) Thyroid (desiccated USP) $\frac{1}{4}$ to 3 gr daily.

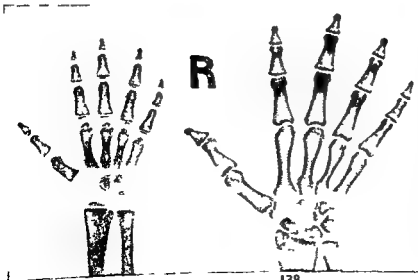


FIG 42 PITUITARY DWARFISM HAND AND WRIST ROENTGENOGRAMS (See Protocol 3 IV Figs 40-41 Chart 16) (Left) Age 8 years Height 40 $\frac{3}{4}$ in Height age 4 $\frac{1}{2}$ years Bone age 2 $\frac{9}{10}$ years (Right) Age 21 Height 50 in Height age 8 years Bone age 17 years



FIG 43 PITUITARY DWARFISM (See Fig 44) Pituitary cachexia at time of initial operation for craniopharyngioma age 12 (Dr Harvey Cushing)



FIG 44 PITUITARY DWARFISM (See Fig 43) Age 39 Height 54 in Patient in coma Rectal temperature 92° F Blood sugar 40 to 50 mg % Note plentiful hair of head and eyebrows Genital atrophy Death occurred with gradual decline in respiration (very shallow) and blood pressure as if passing from hibernation to complete cessation of life Cessation of growth and head aches at 12 years of age relieved by operation Vision in right eye not restored Extreme emaciation at that time Second operation 15 years later for restoration of vision in left eye which was almost completely lost Cystic mass found involving left optic nerve and retrochiasmal region Sight not restored Developed mental confusion and drowsiness Readmitted to hospital 1 year later in coma and died without further attempts to remove cyst or fluid Epiphyses still open Roentgenograms of skull showed calcification 4 cm in diameter in midline and behind the sella with loss of posterior clinoids

SECTION 4

POSTPUBERAL HYPOPITUITARISM

- I DEFINITION** A postpuberal condition resulting from diminished secretions of the anterior pituitary gland generally affecting all hormones in variable degrees but especially the *gonadotropic, thyrotropic and adrenocorticotropic hormones*. Clinically, the condition is best exemplified by the hypopituitarism associated with chromophobe or suprasellar cysts or tumors. Hypothalamic involvement may contribute to the frequent difference between hypopituitarism caused by tumor and that found in Simmonds disease. Some writers make no differentiation, except for etiology and occurrence in females. It must be admitted that the two may be indistinguishable. All cases of chromophobe tumor do not have demonstrable hormonal deficiencies.
- II APPEARANCE** Normal or may retain youthful countenance. Skin smooth and pale. Males take on a female habitus (see Figs 45-49).
- III AGE** Any in postpuberal period^a
- IV SEX** Equal distribution
- V MENTAL DEVIATIONS**
- A INTELLIGENCE** Normal variation
- B RESPONSIVENESS** Normal or slow
- C OTHER ABNORMALITIES** Normal or lapses of memory, somnolence—"pituitary hibernation", psychosis occasionally, rarely insomnia^a
- VI PHYSICAL STATUS**
- A NUTRITION** Good in most cases
- 1 Weight Variable
- 2 Fat distribution Reversion of male type to feminine distribution; may have rapid accumulation around abdomen and hips
- B HEIGHT** Normal unless onset before epiphyseal closure, then retarded
- C EXTREMITIES**
- 1 Upper Normal
- a Hands May be pudgy and somewhat puffy
- b Fingers Tapering fingers unimportant in diagnosis except in contrast with advanced cretinism
- c Span Normal
- 2 Lower Normal
- a Feet Normal variation; swelling occasionally
- b Toes Normal
- D SPINE** Normal

E INTEGUMENT

- | | |
|----------------|---|
| 1 General | Cool, nails brittle ⁸ |
| a Texture | Normal smooth rarely may be caly wrinkling if pituitary myxedema is present |
| b Temperature | Subnormal |
| ■ Moisture | Subnormal |
| d Eruptions | None characteristic |
| ■ Pigmentation | Light brown or yellowish none on mucous membranes no black freckles |
| f Color | Often marked pallor |
| 2 Hair | |
| a Head | Fine thin but abundant, may fall out but only after body hair is gone |
| b Facial | Usually scant in males |
| ■ Axillary | Scant or absent, if removed may not regrow at normal rate |
| d Pubic | Decreased or absent |
| e Body | Decreased or absent including lanugo |

F HEAD

- | | |
|---------------------|--|
| 1 Shape and size | Normal |
| 2 Facial expression | Normal possibly dull |
| 3 Eyes | |
| a General | Normal lids may be swollen nystagmus sometimes |
| b Fundi | Occasionally papilledema frequently optic atrophy of one or both eyes |
| c Visual | |
| (1) Fields | Normal but more often restricted bitemporal hemianopsia homonymous quadrantal achromatopsia with tumor |
| (2) Acuity | Normal or decreased |
| 4 Ears and nose | Normal |
| 5 Mouth and throat | |
| a General | Normal |
| b Teeth | Normal |
| ■ Larynx (voice) | Normal or high pitched |

G NECK

- | | |
|-----------|--------|
| 1 General | Normal |
| 2 Thyroid | Normal |

H CHEST

Normal

I HEART AND PERIPHERAL VESSELS

- | | |
|---------------------------------|---|
| 1 Heart | Normal or diminished size |
| 2 Rate and rhythm | Normal or slow |
| 3 Blood pressure | Normal or low unless onset after previous hypertension ^{3 7} |
| 4 Peripheral arteries and veins | Normal or poor tension |
| 5 Vasomotor | Subnormal response to stimulation |

J BREASTS

- | | |
|----------|--------------------------------------|
| 1 Male | Normal |
| 2 Female | Normal or various degrees of atrophy |

K ABDOMEN

- | | |
|----------|--------------------------------------|
| 1 Liver | Normal |
| 2 Spleen | Normal rarely enlarged ¹⁰ |

3	Hernia	None
4	Tumor	None
L GENITALIA		
1	Male	
a	Penis	Normal or slight regression in size
b	Testes	Variable degree of atrophy ¹⁴
c	Prostate	Atrophic ¹³
2	Female	
a	External	Atrophic
b	Internal	Atrophic
M NEUROMUSCULAR		
1	Muscles	Normal or weakened
2	Gait	Normal or unsteady
3	Body movements	Normal or slow
4	Tremor	None
5	Paresthesias	May occur
6	Reflexes	Hypoactive deep, may be absent
N SPEECH		
		Normal or slow

VII LABORATORY DATA—see 5 VII

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL		
1	Cranial vault	Normal
2	Sella turcica	Normal or enlarged tumor may erode into sphenoid sinus ⁵
3	Mandible	Normal
4	Sinuses	Normal, may have erosion of sphenoid
5	Teeth	Normal
B EPIPHYSEAL STATUS (bone age)		
		Normal unless onset just after puberty then delayed closure
C LONG BONES		
		Normal
D VERTEBRAE		
		Normal
E BONE TEXTURE		
		Normal or osteoporotic
F MISCELLANEOUS		
		May have hypertrophic changes but apparently less often than normal

IX ETIOLOGY

A TUMORS		B MISCELLANEOUS	
1	Craniopharyngioma	1	Pituitary arteries
2	Suprasellar cyst	a	Thrombosis
3	Chromophobe (most common) (see 12)	b	Embolism
4	Acidophilic type in acromegalic patient after	2	Aneurysm of adjacent arteries
a	Intracranial surgery	3	Injury ¹⁷
b	Roentgen therapy	4	Encephalitis
c	Cystic changes	5	Others essentially same as Simmonds disease (see 5 IX)
5	Any growth involving (see Fig 47)	X PATHOLOGY	
a	Pituitary	A GROSS	
b	Hypothalamus	1	Pituitary—as listed under etiology
c	Adjacent areas in brain ¹	2	Thyroid

- a Normal
- b Small (may have increased colloid)
1-13
- 3 Parathyroids—normal
- 4 Adrenals
 - a Normal
 - b Hypoplasia^{1 13}
 - c Atrophy¹
- 5 Testes^{1 1-13}
 - a Normal
 - b Atrophy
- 6 Pancreas
 - a Normal
 - b Atrophy
- 7 Thymus
 - a Small
 - b Enlarged
- 8 Cerebral lesions¹
 - a Infundibular tumor
 - b Glioma
 - c Endothelioma
 - d Hydrocephalus
- 9 Liver
 - a Normal
 - b Fatty changes
- 10 Prostate¹¹
 - a Normal
 - b Atrophy
- B Microscopic
 - 1 Pituitary—variety of lesions—see 2 IV
B 12 a e
 - 2 Testes (see Fig 50)¹³
 - a Leydig cells—absent
 - b Seminiferous tubules
 - (1) Normal
 - (2) Hypoplasia
 - c Sertoli cells—normal
 - d Spermatogenesis
 - (1) Decreased
 - (2) Absent

XI PATHOLOGIC PHYSIOLOGY

—see 5 VI

XII SYMPTOMATOLOGY

- A IF TUMOR AND/OR INTRACRANIAL PRESURE—see 13 VI " " " "
- B GASTRO-INTESTINAL
 - 1 Polydipsia only if neurohypophysis involved
 - 2 Weight rapidly
 - a Increased
 - b Lost
 - 3 Anorexia occasionally

- 4 Constipation
- 5 Hypoglycemic reactions with fasting

C GENITO URINARY

- 1 Polyuria (diabetes insipidus)
- 2 Impotence
- 3 Libido lost
- 4 Amenorrhea
- 5 Sterility

D MISCELLANEOUS

- 1 Cold sensitivity
- 2 Pallor
- 3 Fatigability

XIII DIAGNOSIS

A SYMPTOMATOLOGY

- 1 Hormonal
 - a Amenorrhea (with decreased or absent FSH)
 - b Libido lost in both sexes
 - c Fatigability
 - d Weakness
- 2 When tumor is present
 - a Headache
 - b Visual damages
 - c Somnolence

B SIGNS

- 1 Visual field changes only with tumor
- 2 Optic atrophy with certain growths
- 3 Skin—smooth
- 4 Pallor—often
- 5 Secondary sex characteristics regress in varying degrees

C LABORATORY DATA

- 1 Cholesterol (plasma)—normal (rarely over 230 mg %)
- 2 Basal metabolism rate low (minus 20% to minus 40%)
- 3 Water test—positive
- 4 17 ketosteroids—very low (0.4 mg /24 hrs)
- 5 Sella turcica—usually enlarged

XIV DIFFERENTIAL DIAGNOSIS

A FATIGUE STATES (i.e., chronic nervous exhaustion or anemia)

- 1 The following are usually normal
 - a Menstrual cycle
 - b Libido sexualis
 - c Secondary sex characteristics (male and female)
 - d Visual fields
 - e 17 Ketosteroids
 - f Sella turcica

- 2 Urinary FSH (male and female) is positive in climacteric
- 3 Basal metabolism
 - a Normal
 - b Around minus 20 per cent
- B FUNCTIONAL IMPOTENCE AND FRIGIDITY—All findings as under A
- C AMENORRHEA—see 61 II
- D ANOREXIA NERVOSA—see 5 \IV A
- E SIMMONDS' DISEASE—see 5 \III
- F PRIMARY MYXEDEMA—see 25 \III
 - 1 Skin
 - a Coarse
 - b Dry
 - c Bloated
 - 2 Sex characteristics do not regress
 - 3 Cardiac enlargement
 - 4 Cholesterol (plasma) increased
 - 5 Thyrotropic hormone increased in
 - a Urine
 - b Blood
 - 6 Sella not enlarged unless due to aneurysm of internal carotid

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A CHANGES IN TUMOR
 - 1 Extension
 - a Secondary effects
 - b Intracranial pressure
 - 2 Hemorrhage
 - a Partial blindness
 - b Complete blindness
 - 3 Rupture may improve vision
- B SEQUELAE
 - 1 Pituitary cachexia and/or hibernation
 - 2 Anemia
 - 3 Loss of sexual function
- C ASSOCIATED DISEASES
 - 1 Diabetes insipidus
 - 2 Adrenal insufficiency
 - 3 Diabetes mellitus

XVI TREATMENT

(see 5 \VI for hormonal therapy)

- A INTRA-SELLAR TUMOR (with no indication of extension) (see II below)
 - 1 Roentgen^{4,6,8}
 - a Indication—relief of
 - (1) Intracranial pressure
 - (2) Visual defects
 - (3) Hormonal changes

- b Procedure—see 13 IX A
- Results (see Fig 49)
 - (1) Favorable changes
 - (a) Visual defects
 - [1] Improved
 - [2] Eliminated
 - (b) Normal catamenia rarely returns
 - (c) Headache relieved
 - (d) General improvement in other symptoms
 - (e) Basal metabolic rate may rise (rare)
 - (f) Sella size may decrease (unusual)
 - (2) Chromophobe tumors are often less radiosensitive than chromophil type several courses at least may be required to produce satisfactory results
 - (3) If no improvement occurs after 3 series, over a period of 5 to 6 months then surgery should be considered

2 Surgical

- a Indications
 - (1) Intracranial pressure
 - (2) Visual damage which is
 - (a) Severe
 - (b) Progressive (under observation)
 - (3) Neurologic complications—see ventriculography 2 \III F 6
 - (4) No result from roentgen therapy
- b Procedure—see 13 VII
- c Results—see roentgen therapy A 1 c above
 - (1) Tumor may recur
 - (2) Visual damage may become worse
 - (3) Operative fatalities in 5 to 10 per cent
- B EXTRASELLAR TUMOR (or with intrasellar tumor extension)
 - 1 Ventriculography or encephalography indications—to determine tumor
 - a Size
 - b Location
 - 2 Roentgen
 - a Indication—if tumor is
 - (1) Inaccessible
 - (2) Radiosensitive
 - b Procedure—see 13 IX A

- 3 Surgical
 - a. Indications
 - (1) Tumor extirpation
 - (2) Biopsy
 - b Procedure—see 13 VII A

XVII PROGNOSIS

A INTRASELLAR TUMOR (see 12 IV)

- 1 With roentgen therapy
 - a Visual field improvement in large percentage
 - b Headaches partially relieved
 - c Menstrual periods may return (rarely)
- 2 With extirpation of the tumor
 - a Intracranial pressure—decreased
 - b Visual fields—improved

- c Secondary sex characteristics—not altered
- d Anemia—the same
- e Tumor may recur in
 - (1) Small percentage
 - (2) Malignant types

B SUPRASELLAR CYST OR TUMOR

- 1 Relief of headache
- 2 Improvement in visual fields with therapy
- 3 Endocrine status shows little or no improvement

C INACCESSIBLE TUMOR—Poor outcome

XVIII CAUSES OF DEATH

A COMPLICATIONS FROM TUMOR

B PNEUMONIA

CHROMOPHOBE ADENOMA

Family history Allergy

Past medical Pneumonia and empyema 2 years ago

Chief complaint Losing weight

History of present illness Patient has had frequent colds since pneumonia. Anemia for 4 years BP low for years

Physical examination Age 23 male single
Weight 117 lbs Height 67 in BI 98/58
Fallor

Laboratory data RBC 4,070,000 Hgb 11.7 Gm or 75% WBC 5056 Differential normal

Roentgenographic findings Old empyema with thickened pleura

Treatment Iron

Progress

YEARS LATER

- 5 Patient was inducted into military service where he developed visual disturbances tingling in his fingers leg cramps and generalized weakness Skull roentgen film showed an enlarged sella turcica diagnosis pituitary adenoma Visual fields showed evidence of slight concentric constriction BMR minus 30 to minus 35% Roentgen therapy instituted (Testicular biopsy—see below) Testosterone pellets 450 mg inserted Methyltestosterone 10 mg orally tid for 2 yrs then 1 tablet daily Also iron and vitamins

PROTOCOL V FIGS 49 50

- 8 *History* Feels well Libido improved Erections each morning and about every 4 to 5 days Penis seems larger Shaves every second day Does not fall asleep any more More strength No change in hair

Physical examination Weight 144 lbs Height 67½ in Pulse 68 BP 110/85 No axillary hair Scant pubic hair Beard sparse Slight prominence of breasts Penis small Testes firm Sella measures 15 x 20 mm or 260 sq mm No sperm cells in ejaculated specimen
Laboratory data RBC 4,890,000 Hgb 85%

GLUCOSE TOLERANCE TEST

Hour	Blood sugar mg %	Serum phosphorus mg %
0	86	3.9
	123	3.3
2	80	3.1
3	61	3.1
4	74	3.3

ADRENAL WATER TEST

Urine volume	
10 00 P M—7 30 A M	120 cc
8 00 A M Water intake 140 oz	
9 00 A M	24 cc
10 00 A M	16 cc
11 00 A M	24 cc
12 00 NOON	16 cc

- 9 - Chorionic gonadotropin—2,000 units, 5 times a week, was administered for a period of 3 months. No spermatozoa had been found previously, during or after this treatment. Rather rapid, tender, nodular enlargement of breasts occurred with this medication. Patient gained 3 lbs. Libido was maintained without testosterone.

Comment An example of anemia of obscure origin which eventually was found to be due to hypopituitarism. Patient had loss of libido but did not complain or refer to this, nor did the examining physician inquire about it. The diagnosis was not made until visual disturbance developed. Hyaline change in testes might have been prevented by earlier recognition and treatment. Chorionic gonadotropin maintained sexual function without testosterone did not produce spermatogenesis but caused gynecomastia (see 51 V I E 5).

Testicular biopsy

Seminiferous tubules

- Number per low power field—70 to 80
Width—one half to one third of normal, distribution uniform
Sertoli cells—present at the narrow lumen
Cells of spermatogenesis—absent or a few spermatogonia (?)
Basement membrane—thin normal. High layer of hyaline mass within the tubules (not around them), between the basement membrane and the Sertoli cells. This layer occupies about half of the tubular space, internal thickening of the basement membrane or intratubular exudate of this membrane and not of the Sertoli cells.

Leydig cells—absent

- Interstitial tissue—widened, loose, hyalinized
Blood vessels—normal, congested

Comment Absence of Leydig cells and tubular hypoplasia are typical of hypopituitarism. The hyaline exudate above basement membrane is unusual.

REFERENCES

- 1 Beckmann J W and Lubie L ■ A clinical study of twenty one cases of tumor of the hypophyseal stalk. *Brain* 52 127-170 (July) 1929
- 2 Cushing H. Pituitary Body and Its Disorders pp 42-84 Philadelphia Lippincott 1912
- 3 — Neurohypophyseal mechanisms from clinical standpoint (Lister memorial lecture). *Lancet* 2 119 (July) 1930
- 4 Davidoff L M and Fering E H - Surgical treatment of pituitary tumor. *Am J Surg* 75 99-136 (Jan) 1948
- 5 Henderson W ■ Sexual dysfunction in adenomas of the pituitary body. *Endocrinology* 15 111-127 (Mar-Apr) 1931
- 6 Hirsch O. Surgery a contribution to our knowledge of pituitary function. *Confinia neurol* 7 45-54 (Jan) 1946
- 7 Holmes G. Pituitary disorders. *Brit M J* 2 1035-1040 (Dec) 1926
- 8 Horrax G, Hare H F, Younghusband O and Hurthall L M. Unpublished data.
- 9 Hurthall L M and Younghusband O. Diagnosis of chromophobe tumor (presumed or verified). *Radiology* 52 179-185 (Feb) 1949
- 10 Hurthall L M. Unpublished data.
- 11 Jones H M. Possible anatomic relations between pituitary body and prostate gland: the pathologic pituitary body. *J Urology* 42 50-56 (July) 1939
- 12 Lerman J and Means J H. Hypopituitarism associated with epilepsy following head injury: report of 2 cases. *J Clin Endocrinol* 5 119-131 (Mar) 1945
- 13 McGavack T H, Saccione A, Vogel M and Harris R. Craniopharyngioma with panhypopituitarism: case report with clinical and pathological study. *J Clin Endocrinol* 6 716-796 (Dec) 1946
- 14 Starr P and Davis L. Endocrine studies of patients after subtotal hypophysectomy. *Illinois M J* 78 486-492 (Dec) 1940

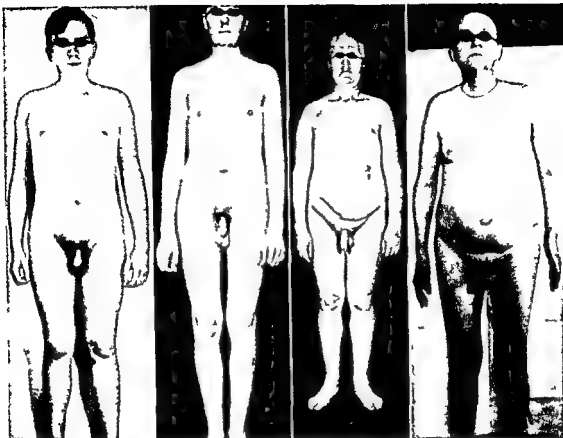


FIG 45 HYPOPITUITARISM DUE TO PITUITARY TUMOR These four cases illustrate the variation in body contours and hair distribution in definite hypopituitarism. Dependence on external characteristics alone is unreliable. All these patients had cranial surgery.

(Extreme left) Panhypopituitarism—chromophobe tumor (verified). Chief complaints: Headache and failing vision. Physical examination: Age 20 male, hemianopsia, no beard, body hair present, female escutcheon, enlarged liver and spleen. Laboratory data: RBC 4.3 million, Hgb 78%, plasma cholesterol 191 mg %, BMR minus 32%. Roentgenographic findings: Enlarged sella, open radial epiphyses. Treatment: Cranial surgery.

(Left of center) Panhypopituitarism—mixed tumor (verified). Chief complaint: Failing vision. Physical examination: Eyes blind right 50%, in left. Skin soft and smooth. Hair silky and fine. Axillary and body hair normal. Female escutcheon. Genitalia slightly below normal. Laboratory data: RBC 4.0 million, Hgb 77%, BMR minus 29%. Treatment: Operation. Verified mixed type of tumor, predominantly eosinophilic, in spite of obvious hypopituitarism.

(Right of center) Panhypopituitarism—chromophobe tumor (verified). Chief complaint: Blurred vision, occipital headache, fatigue, loss of libido. Physical examination: Age 47 male, note body contour, female or girdle type of obesity and slight prominence of breasts, most likely due to deficient gonadal secretion rather than the direct result of pituitary hypofunction; axillary hair present, body hair decreased, female escutcheon. Laboratory data: RBC 3.6 million, Hgb 84%, plasma cholesterol 230 mg %, BMR minus 24%. Treatment: Restoration of vision with roentgen therapy, satisfactory sexual function with testosterone pellets.

(Extreme right) Panhypopituitarism—cystic chromophobe tumor. History of present illness: Baldness present before onset of disorder, loss of all other hair, mental depression, confusion, somnolence, weakness, and anemia for 6 years; partial loss of vision for 4 years; headache for 1 year. Physical examination: Age 64 male, Eyes right blind, left 25%, loss of vision. Note fat distribution and prominence of breasts. Laboratory data: RBC 4.6 million, Hgb 83%, plasma cholesterol 378 mg %, BMR minus 8%. Treatment: Cranial surgery.



FIG 46 PITUITARY TUMOR EXERTING EFFECT AROUND THE AGE OF 15

History Normal sexual development began between 12 and 13. At 15 voice changed, he began to shave and continued to do so about 3 or 4 times a year. Growth stopped at 18. Libido normal.

Chief complaint Blurred vision in left eye of 6 months duration.

Physical examination Age 21, male, weight 337 lbs, height 76½ in, span 77 in, BP 156/100. Normal body and axillary hair except for female escutcheon; testes and penis but buried in fat.

Laboratory data RBC 4.5 million, Hgb 13.2 Gm.

Roentgenographic findings Skull: no evidence of acromegaly; sella measured 26 x 23 mm with extension into sphenoid sinus. Epiphyses of hands, wrists and iliac crests were closed.

Comment No follow up. Although no further studies could be made, it is obvious from the history that little glandular deficiency was present. Presence of tumor did not take place until the age of 15 at least. Family history reveals the background for his size: Father 76 in and large, mother 68 in and stocky. Patient's obesity and over height always has been present. Only evidence of glandular deficiency was the infrequency in shaving. It is not known if a male escutcheon ever had been present. The relationship of his body configuration to the pituitary tumor is difficult to assess.

FIG 4: HYPOPITUITARISM
—GANGLIOMELOMA (verified)

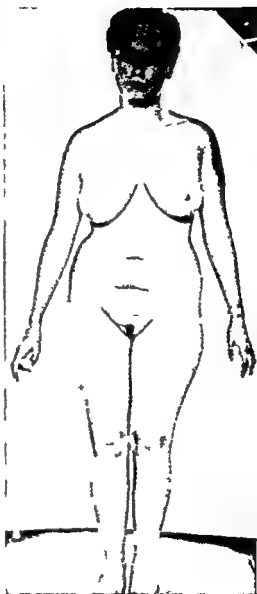
Chief complaints Blurring vision always had oligomenorrhea until onset of amenorrhea and hot flashes 3 years before entry absence of libido recent loss of axillary and pubic hair

Physical examination Age 28 female weight 123 lbs height 59 in bitemporal upper quadrant defects in visual fields fine pale skin infantile cervix

Laboratory data Plasma cholesterol 4 mg %
BMR minus 4%

Röntgenographic finding
Sella enlarged

Comment Craniotomy with death from hyperthermia Tumor adhered to optic nerves and third ventricle Hot flashes were experienced with evidence of (neurogenic?) hypopituitarism Patient observed before hormone assays were done



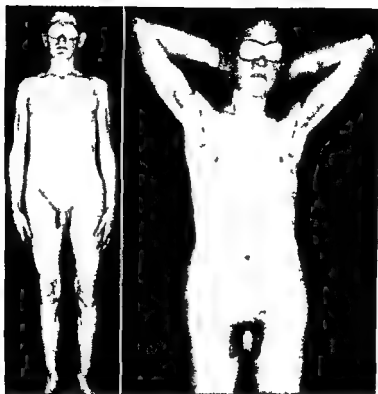


FIG. 48 : PANHYPOPITUITARISM — CHROMOPHOBE TUMOR (verified)

(Left) Age 36

Chief complaints : Failing vision loss of libido sense of smell and body hair

Findings : Bitemporal hemianopsia RBC 4 200 000 Hgb 81% Plasma cholesterol 326 mg % BMR plus 9%

Operation : Restoration of vision rapid recurrence of tumor with failing vision in spite of postoperative radiation : successful reoperation with normal vision Persistent hypopituitarism Unable to tolerate 2 gr of thyroid (desiccated USP) daily because of marked weakness

Treatment with testosterone maintained strength 300 mg in pellets lasting from 3 to 4 months 30 mg of methyltestosterone orally and testosterone in glycol alcohol sublingually also effective Hemoglobin unchanged by any form of anti-anemic therapy

(Right) Growth of hair can be seen in left axilla only and greater amounts on the left pubic area from local injection of testosterone in glycol alcohol Seven mg were used daily over a period of 5 months along with 10 mg sublingually for the last 2 months of the same period Excellent response with 15 to 20 mg of Cortisone daily

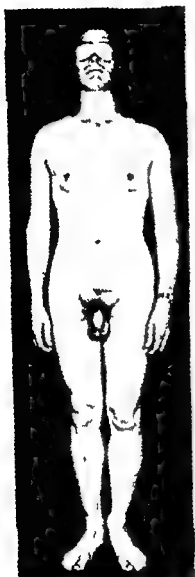


FIG 49 CHROMOPHOBE TUMOR (See Protocol 4 \ Fig 50) Treatment with roentgen therapy testosterone and chorionic gonadotropin The last caused rapid enlargement of breasts With absence of tubular function gynecomastia may have resulted by factors postulated in Klinefelter's syndrome

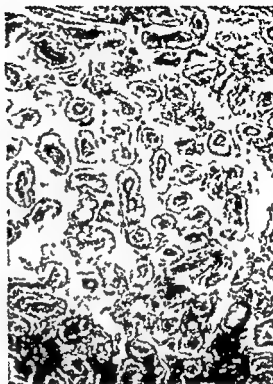


FIG 50 TESTES IN HYPOPITUITARISM (See Protocol 4 \) Note tubular atrophy and absence of Leydig cells (See Fig 49 for details)

SECTION 5

SIMMONDS' DISEASE

SYNONYMS Cachexia hypophysopriva, Apituitarism, Sheehan's disease

I DEFINITION

A clinical entity characterized by almost total abolition of all the pituitary secretions, which may be rightfully termed apituitarism. The distinction between this disorder and panhypopituitarism is only a matter of degree. The majority of the cases with chromophobe or other tumors do not approach the clinical state described originally by Simmonds^{80, 91}. The greater degree of anorexia and resulting malnutrition may contribute a large part to the clinical findings in Simmonds' disease as compared with other hypopituitary states. Percentages listed below are cited from Escamilla and Lissner (1942)²⁵.

II APPEARANCE

Normal early, but eventually in some extreme wasting, emaciation, presenescence and retrogression of primary and secondary sex characteristics (see Protocol 5 VI)

III AGE

9 to 69, average 41 years

IV SEX

Females predominate, ratio 7:4

V MENTAL DEVIATIONS

A INTELLIGENCE

Average or subnormal in some cases

B RESPONSIVENESS

Normal or slow, apathic, stuporous

C OTHER ABNORMALITIES

Melancholia, disorientation and often psychosis (over 50%)

VI PHYSICAL STATUS (see Figs 51, 53, 56 and 58)

A NUTRITION

May be exceedingly poor, 'skin and bones,' but relatively good in many

1 Weight

Very marked loss or slight amount, average 44 lbs⁸⁰

2 Fat distribution

Both visceral and subcutaneous fat reduced, often completely gone¹⁰⁷

B HEIGHT

Normal unless onset before epiphyseal closure, then retarded

C EXTREMITIES

1 Upper

Normal or evidence of extreme cachexia with prominence of all skeletal parts

a Hand

May appear small

b Fingers

Occasionally cyanotic, nails brittle

c Span

Normal

2 Lower

Normal or wasting of muscles and fat with exaggeration of bony skeleton

a Feet

Normal

b Toes

Normal, may show vasomotor and trophic disturbances

- D SPINE** Normal or bony structures very evident
- E INTEGUMENT**
- 1 General Senile changes folds of skin which have been raised remain standing trophic disturbances^{7 11}
 - a Texture Smooth or senile
 - b Temperature Vasomotor disturbances body temperature low—often 95° to 96.8° F (35°C)²¹
 - c Moisture Absent secretion of sudiferous and sebaceous glands abnormally dry skin occasionally
 - d Eruptions None characteristic
 - Pigmentation May show light brown or yellow pigment (24%) none of mucous membranes no black freckles
 - f Color Often marked pallor (48%)
 - 2 Hair
 - a Head Normal or prematurely gray may fall out sparse (50%)
 - b Facial Usually scant in males (50%)
 - c Axillary Falls out (80%) if removed may regrow at normal rate
 - d Pubic Falls out (80%)
 - e Body Decreased or absent including lanugo
- F HEAD**
- 1 Shape and size Normal or small features
 - 2 Facial expression Wizenod pathetic or not unusual
 - 3 Eyes
 - a General Normal may appear deep sunken or lifeless
 - b Fundi Normal if tumor present usually optic atrophy²²
 - c Visual
 - (1) Fields No defects unless due to tumor then usually partial or complete defects bitemporal hemianopsia
 - (2) Acuity Normal or decreased depending on optic findings and progression of severe cachexia
 - 4 Ears and nose Normal
 - 5 Mouth and throat
 - a General Normal may show signs of vitamin B deficiency (smooth beefy tongue cheilosis)
 - b Teeth Canines fall out easily (42%)^{7 23}
 - c Larynx (voice) May be weakened with progression of disease
- G NECK**
- 1 General Thin scrawny chickenlike all underlying structures may be evident
 - 2 Thyroid Small but may be prominent because of tissue wasting
- H CHEST** Thoracic cage is normal or shows all its bony landmarks pleural fluid rarely
- I HEART AND PERIPHERAL VESSELS**
- 1 Heart Size may be smaller than normal (hypoplastic) tones weak distant rarely pericardial effusion²⁴
 - 2 Rate and rhythm Bradycardia
 - 3 Blood pressure Hypotension usually may have slight increase or normal average 96/62²⁵
 - 4 Peripheral arteries and veins Poor tension
 - 5 Vasomotor Subnormal response to stimulation

J	BREASTS	
1	Male	Normal
2	Female	Various degrees of atrophy
K	ABDOMEN	Ascites may be present ⁷²
1	Liver	Not palpable
2	Spleen	Not palpable
3	Hernia	None
4	Tumor	None
L	GENITALIA	
1	Male	
a	Penis	Normal or regression in size
b	Testes	Variable degrees of atrophy
c	Prostate	Atrophic
2	Female	
a	External	Atrophic
b	Internal	Atrophic
M	NEUROMUSCULAR	
1	Muscles	Marked weakness and atonia eventually
2	Gait	Normal or slow and with difficulty, later bedridden
3	Body movements	Normal or labored if extreme cachexia and muscular atonia
4	Tremor	None
5	Paresthesias	Possible
6	Reflexes	Normal or hypoactive
N	SPEECH	Normal or slow

VII LABORATORY DATA

A	URINE	
1	General	Normal or small amount (unless diabetes insipidus)
2	Special analyses	
a	Sugar	None
b	Albumin	May be present
c	Nitrogen	Normal
d	Creatine	Normal or slight decrease
e	Creatinine	Normal or slightly increased
f	Sodium	Normal
g	Potassium	Normal
h	Calcium	Normal
i	Phosphorus	Normal
j	Iodine	Decreased ⁸⁴
B	HEMATOLOGY	
1	Red blood cells	Normal or decreased in prepuberal hypopituitarism usually decreased 3 to 4 million in adults (see Protocol 5 V) ⁸⁵
2	Hemoglobin	Normal or decreased in prepuberal cases; Simmonds' disease in adults average 65 per cent chromophobic tumor average 85 per cent (see 13 III B) ⁸³
3	White blood cells	Normal or decreased ^{75 87 89 91}
4	Differential	Monocytes or microcytes eosinophils increased (average 6.3% in Simmonds' disease) relative lymphocytosis and neutropenia ^{8 77 8 87 89}
5	Color index	Normal or decreased ⁸⁹

C BLOOD CHEMICAL ANALYSES

1 Sugar	Normal, ¹¹¹ but more often decreased, average 66 mg % (Simmonds disease)
2 Nonprotein nitrogen	Normal or slightly decreased
3 Protein	Normal or decreased
4 Uric acid	Normal or decreased ¹⁰ 103
5 Cholesterol	Normal or decreased, increased occasionally ¹⁸ 1 71 203 23 30 41 73 87 84 96 110 11
6 Sodium	Normal or decreased ¹¹ 31 31 46 88 110 112
7 Potassium	Variable ²⁵ 36 84 11
8 Calcium	Normal ¹⁴ 93
9 Phosphorus	Normal or decreased ¹⁰ 9 84 96
10 Phosphatase	Normal or increased ¹⁰
11 Chlorides	Normal, occasionally decreased ⁷⁷ 63 90
12 Iodine	Low organic values 84 9 11 113
13 Creatine	Normal ¹³
14 Creatinine	Normal or increased slightly ¹³
15 Carotin	Present ¹ -5

D FUNCTION TESTS

1 Tolerance (see Chart 17)	
a Glucose	Increased usually (see Table 102 p 1426) ¹¹ 1 3 71 83-87 49 50 57 58 61 66-70 79 84 87 88 83 8 84 107 110 117 114
b Glucose insulin	Insulin sensitivity increased ¹ 11
c Insulin	Normal, delayed or absent rise in blood sugar ¹⁴ 31 3 54 60 71 87 9 102, 112, 113
d Galactose	Normal or high curve ¹⁰⁹
e Iodine	Decreased possibly
2 Adrenal water	Positive usually ²⁸ 79 86
3 Salt deprivation	Positive or may be negative ⁷⁷ 30 34 62 79 80 83 87 113
4 Balance	
a Nitrogen	Probably negative but difficult to determine ⁸⁰ 110 113
b Calcium	Probably negative but difficult to determine

E MISCELLANEOUS

1 Basal metabolic rate	Rarely normal usually very low (average minus 35% in Simmonds disease ³⁰ 117)
2 Circulation time	Normal or increased ¹⁰⁰ 61
3 Sedimentation rate	Variable ⁴²
4 Specific dynamic action of protein	Normal or decreased (because of lowered BMR) ⁷³ 71 31 79 113
5 Gastric analysis	Normal or achylia ³¹ 35 6 68 69 83 11
6 Electrocardiogram	Normal unless myxedema ⁴³
URINARY HORMONE ASSAYS	
1 FSH	Negative (usually less than 6 mu) ¹ 18 72 23 31 40 41 48 54 55 68 89 84 107 111 rarely may be positive with chromophobe tumor ⁴³
2 LH	No data
3 Estrogens	Decreased or absent ¹⁸ 36 43 48 49 53 65-68 88
4 Pregnanediol	Absent ⁴³
5 17 ketosteroids	Absent or very low ¹ 88 27 31 33 88 36 40 88 54 60 68 83 107 10 106 88
6 11-oxysteroids (glycogenic units)	Very low or absent ¹⁶ 61 88 107 74

7	Aschheim Zondek	Negative
8	TSH	Decreased or absent ^{10 40 41 89 112}
9	Corticotropins	Absent ⁴⁰
G	BIOPSY	
1	Endometrial	Hypoplasia or atrophy
2	Testicular ¹³	
a	Tubules	Hypoplastic or atrophic
b	Leydig cells	Absent
c	Spermatogenesis	Arrested
H	VAGINAL SMEAR	Atrophic, variable amounts of glycogen ⁴³
I	SEMEN ANALYSIS	Aspermia

VIII ROENTGENOGRAPHIC FINDINGS

A	SKULL	
1	Cranial vault	Normal
2	Sella turcica	Normal enlarged or unusually small ; occasionally intra sellar or suprasellar calcareous deposits destruction possible ^{2 29 83 101}
3	Mandible	Normal ^{80 9 110}
4	Sinuses	Normal, underdeveloped in prepuberal cases
5	Teeth	Carious in some cases, normal dental age in prepuberal hypopituitarism ⁴³
B	EPIPHYSEAL STATUS (bone age)	Normal, retarded if onset before adolescence (see Fig. 57) ^{4 43}
C	LONG BONES	Normal
D	VERTEBRAE	Normal, decalcification reported ¹¹
E	BONE TEXTURE	Normal
F	MISCELLANEOUS	None

IX ETIOLOGY⁷⁵

A	FOLLOWING PREGNANCY (see Figs 53 and 58)	9 Dysentery
1	Puerperal sepsis	10 Encephalitis
2	Prolonged and difficult labor with or without severe hemorrhage (see Protocols 5 VII to V)	11 Catarrhal jaundice
3	Repeated conceptions	12 Tuberculosis ³
4	Toxemia	13 Syphilis
B	INFECTIOUS PROCESSES (not associated with pregnancy)	C MISCELLANEOUS
1	Meningitis	1 Postoperative hypophysectomy
2	Pulmonary infection	2 Aneurysm of adjacent arteries ⁴³
3	Tularemia	3 Skull fracture with
4	Malaria	a Hemorrhage at midbrain
5	Influenza	b Posttraumatic arteriovenous aneurysm ⁵⁸
6	Osteomyelitis	4 Tumors
7	Diphtheria	a Primary
8	Rheumatic fever	(1) Intracellular
		(2) Extracellular
		b Secondary metastatic
		5 Old age ⁵⁷
		6 Intensive pituitary radiation (rare)
		7 Idiopathic (see Fig 56)

X PATHOLOGY²³

A GROSS

1 Pituitary

- a Normal gland occasionally, but always associated with definite pathology at
 - (1) Tuber cinereum
 - (2) Hypothalamus

- b Necrosis (Sheehan's disease) frequently develops after postpartum following^{19 1 9 71 87 94}

- (1) Ischemia
- (2) Embolic infarction

- c Atrophy

- d Cyst of Rathke's pouch or craniopharyngioma

- e Hemorrhage

- f Thrombosis

- g Aneurysm

- h Neoplasms

- (1) Primary
 - (a) Pituitary (unusual)
 - (b) Extrasellar
 - [1] Infundibular
 - [2] Glioma
 - [3] Endothelioma
- (2) Secondary (metastatic)

- i Sclerosis

- j Fibrosis

- k Abscess

- l Inflammations

- m Adenomas

- (1) Chromophobic
- (2) Basophilic

- n Tuberculosis (rare)

- o Syphilis (uncommon)

- 2 Other organs—generally show signs of atrophy and/or fibrosis (splanchnomicria)

B MICROSCOPIC

- 1 Pituitary—see 2 IX B

- a Findings depend on gross pathology
- b If any pituitary cells remain they are⁸⁷
 - (1) Mostly chromophobes
 - (2) Few chromophils

- 2 Bone marrow¹⁰³

- a Inactive
- b Eosinopenia

XI PATHOLOGIC PHYSIOLOGY

A GROWTH HORMONE

- 1 It is unknown if this hormone is elaborated in a normal person after longitudinal development ceases
- 2 If this is true a deficiency or absence of growth hormone must play a role in the hypopituitary state causing some anabolic failure

B GONADOTROPIC HORMONES

- 1 Degree of decreased function is variable
- 2 Usually first hormonal deficiency to be manifested clinically

C THYROTROPIN

- 1 Secretion reduced
- 2 Pituitary myxedema is rare

D ADRENOCORTICOTROPIC HORMONE

- 1 Secretion is decreased generally
- 2 Severe crises of Addison's disease are rare possibly due to a higher functional level in the latter of the⁴³
 - a Pituitary
 - b Thyroid
- 3 Axillary, pubic or facial hair may persist with an absent or ineffectual gonadotropin secretion (even with a pituitary tumor) due to some adrenal secretion
- 4 Adrenal water test may still be positive

E PREDOMINANT HORMONAL DEFICIENCIES

- 1 Selective deficiency of one pituitary hormone is exemplified by FSH negative eunuchoidism
- 2 Predominant deficiency of one or more hormones in panhypopituitarism seems likely (see 6 7)

F MISCELLANEOUS

- 1 Cachexia due to marked or complete deficiency of pituitary hormones is a complex problem in this disease
- 2 Anorexia undoubtedly contributes to final state through inadequate (see 103 XIV)
 - a Nutrition
 - b Vitamins
 - c Amino acids
 - d Enzymes
- 3 Carbohydrate metabolism (see 103 I J 1)
 - a Tolerance greatly increased
 - b Liver glycogen deposition enhanced

c Insulin secretion is apparently unchanged

G REGENERATION OF PITUITARY TISSUE

- 1 Postpartum necrosis of pituitary may be followed by regeneration of tissue, especially if subject becomes pregnant (unlikely)⁸⁸
- 2 This does not occur with other pathologic changes

XII SYMPTOMATOLOGY

A COMMENT

- 1 If tumor and/or intracranial pressure—see 13 VI
- 2 Many of the following symptoms do not occur initially, but may develop gradually with progression of the disorder

B NEUROMUSCULAR

- 1 Wasting, marked
- 2 Cachexia
- 3 Fatigue, excessive
- 4 Weakness
- 5 Prostration
- 6 Muscular
 - a Atonia
 - b Atrophy
- 7 Headache
- 8 Vertigo
- 9 Fainting
- 10 Cold sensitivity
- 11 Dull
- 12 Drowsiness
- 13 Confusion
- 14 *Disorientation*
- 15 Depression
- 16 Irritability
- 17 Coma (hypoglycemia 5%)

C GASTRO INTESTINAL

- 1 Anorexia, marked
- 2 Dyspepsia
- 3 Constipation
- 4 Diarrhea
- 5 Abdominal pain
- 6 Vomiting
- 7 Weight loss (not diagnostic)

D GENITO URINARY

- 1 Amenorrhea
- 2 Loss of libido
- 3 Impotence
- 4 Genital atrophy
- 5 Sterility
- 6 Polyuria
- 7 Oliguria

XIII DIAGNOSIS

A COMMENT—The early diagnosis may be difficult but is to be entertained if a majority of the following are found

B SYMPTOMATOLOGY

- 1 History of severe past illness, especially postpartum hemorrhage (see 5 IX A)¹⁴
- 2 Amenorrhea
- 3 Sexual function lost
- 4 Cachexia, varying degree

C SIGNS

- 1 Hypotension
- 2 Skin is smooth
- 3 Pallor
- 4 Sexual hair is shed

II LABORATORY DATA

- 1 Blood count
 - a Anemia
 - b Relative lymphocytosis
 - c Eosinophilia
- 2 Glucose tolerance—increased
- 3 Insulin sensitivity—increased
- 4 Water test—positive
- 5 ACTH test—variable
- 6 Basal metabolic rate—low
- 7 17 Ketosteroids
 - a Low
 - b Absent

XIV DIFFERENTIAL DIAGNOSIS

A ANOREXIA NERVOSA (see Fig 55)¹⁰

- 1 The eventful extreme undernutrition in many cases leads to a physiologic failure of the anterior pituitary, which is often indistinguishable from "organic" hypopituitarism
- 2 The following data may be helpful in solving the problem
 - a Type of individual
 - (1) Young (average age 21)
 - (2) Single
 - (3) Females predominate (ratio 9 1)
 - b History of
 - (1) Mental shock
 - (2) Psychosis
 - (3) Inferiority complex
 - (4) Postpartum hemorrhage may not be obtained
 - (5) Asthenia which is not as severe
 - c Precocious senescence is less evident (5%)

- d Weight
 - (1) Changes are not diagnostic
 - (2) Patient may secretly discard feedings
- e Skin shows less change may be
 - (1) Rough
 - (2) Scaly
- f Pallor—usually absent
- g Temperature may be subnormal (15%)
- h Hair—less frequently affected (15%) at
 - (1) Pubis
 - (2) Axillae
- i Teeth do not
 - (1) Decay
 - (2) Fall out
- j Breasts—atrophy proportionately
- k Eosinophilia—absent
- l Chlorides (serum)—decreased¹⁰⁰
- m Water test
 - (1) Normal (mild cases)
 - (2) Positive (severe cases as in Simmonds disease)
- n Response to ACTH test
- o Lower values than Simmonds disease for
 - (1) 17 ketosteroids
 - (2) Cortin (glycogenic units)
- p Sella never is
 - (1) Deformed
 - (2) Calcified
- q Average duration 2 ½ years
- r Response to adequate nutrition
 - (1) Final diagnostic sign in many
 - (2) Patient may require
 - (a) Tube feedings
 - (b) Intravenous fluids
 - (c) Vitamin supplements
- s Simultaneous hormone therapy as used in Simmonds disease
 - (1) Recovery may be hastened
 - (2) Unnecessary to continue with this if sufficient caloric intake can be maintained
- t Comment
 - (1) Anorexia nervosa may be indistinguishable from Simmonds disease (see Protocol 5 VIII)
 - (2) If recovery is obtained by any means and maintained subsequently on adequate nutrition only a diagnosis of anorexia nervosa is then justified

II PRIMARY MYXEDEMA (see 25 VIII)

- 1 Weight loss is not common
 - 2 Hair
 - a Very fine
 - b Scant
 - 3 Face
 - a Bloated
 - b Puffy
 - 4 Edema nonpitting
 - 5 Heart size may be increased
 - 6 Secondary sex characteristics usually not affected
 - 7 Genital organs show no atrophy
 - 8 Cholesterol (plasma)—high
 - 9 Water test—normal, occasional exception¹³
 - 10 Electrocardiogram—abnormal
- ## C ADDISON'S DISEASE
- 1 History of
 - a Tuberculosis in many patients
 - b Remissions
 - (1) Vomiting
 - (2) Diarrhea
 - c Acute crises
 - 2 Catamenia is present in majority
 - 3 Presenescence is not found
 - 4 Black freckles
 - 5 Pigmentation of
 - a Mucous membranes
 - b Exposed areas
 - c Parts subject to friction
 - 6 Hair is less affected
 - a Beard
 - b Axillary (infrequently lost)
 - c Pubic (rarely falls out)
 - d Body
 - 7 Lymph glands are palpable
 - 8 Hematocrit—increased
 - 9 Water test—positive
 - 10 No response to ACTH test
 - 11 Basal metabolic rate
 - a Normal
 - b Decreased slightly
 - 12 Urinary FSH—increased if after menopause
 - 13 17 ketosteroids
 - a Variable
 - b Subnormal usually
 - 14 Sella—normal
 - 15 Adrenals may be calcified

D TUBERCULOSIS

- 1 Lesion may be located
- 2 Febrile course
- 3 Aging not evident

- 4 Advanced stages diagnosis obvious
- 5 Tubercle bacillus often isolated
- 6 Negative results for adrenal insufficiency, except possibly the water test
- 7 17 ketosteroids—more normal

E MALIGNANCIES

- 1 Lesion often discovered
- 2 Presenescence absent
- 3 Obvious in advanced stages
- 4 17 ketosteroids—normal

F HYPERTHYROIDISM (see 26 VIII)

- 1 Skin
 - a Moist
 - b Warm
- 2 Sexual hair—normal
- 3 Thyroid gland—enlarged
- 4 Blood pressure—normal for age
- 5 Pulse pressure—wide
- Sexual organs—normal
- 7 Tremor—present
- 8 Cholesterol (plasma)—low
- 9 Iodine (blood)—increased
- 10 Basal metabolic rate—elevated
- 11 Hyperthyroidism and Addison's disease may coexist

G ANEMIAS

- 1 Skin texture—normal usually
- 2 Hair growth—not affected
- 3 Sexual organs—normal
- 4 Basal metabolic rate—normal in most cases
- 5 Sprue
 - a Liver and/or spleen may be palpable
 - b Macrocytic anemia
 - c Stools
 - (1) Fatty
 - (2) Loose
 - d Calcium (serum)—may be low
 - Water test—positive
- 6 Pernicious anemia (rarely associated disease)⁴⁹
 - Spleen and/or liver may be palpable⁵⁰
 - b Macrocytic anemia
 - c Posterior lateral column degeneration possible
 - d Urobilinogen excretion—increased
 - e Response to liver injections

H OTHER DISEASES

- 1 Pellagra

- a Hair—normal
- b Dermatitis—common at exposed surfaces
 - Sexual organs—normal
- d Basal metabolic rate—normal
 - Response to therapy
- 2 Pituitary myxedema (see 6)
 - a Cholesterol (plasma)—high
 - b Electrocardiogram may be
 - (1) Normal
 - (2) Abnormal
- 3 Chronic ulcerative colitis or ileitis
 - a Diarrhea
 - b Lesion can be localized
 - Fever
 - d Fingers clubbed
 - Secondary effects of pituitary dysfunction may be present
 - f Sedimentation rate—increased
 - g Water test—positive as in Simmonds disease

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A INTERCURRENT INFECTIONS

B HYPOLYCEMIC ATTACKS⁵¹

C DIABETES INSIPIDUS⁵²

D ADRENOCORTICAL CRISES—May occur depending on degree of secondary adrenocortical atrophy

E DIABETES MELLITUS (rare)⁵³

F PERNICIOUS ANEMIA (infrequent)⁵⁴

G ARTHRITIS hypertrophic or rheumatoid (see Fig 54)

XVI TREATMENT

A OBJECTIVES

- 1 Substitution for the various glandular deficiencies to
 - a Improve patient's strength
 - b Prevent hypoglycemic reactions
 - c Restore sexual function (of secondary importance)
- 2 If pituitary tumor is present (and following the above program)
 - a Roentgen therapy to decrease its size (see 13 IV.)
 - b Surgical removal if indicated (see 13 VII)

B GENERAL MANAGEMENT

- 1 Growth hormone
 - a Dosage—intramuscular, 10 ru (1 cc) or more daily

b Comment

- (1) Theoretically might be helpful because of anabolic effects
- (2) Pure growth hormone is not available commercially

2 Testosterone⁹ 1 35 46 54 110 113

a Indications

- (1) Advisable in most cases with initial treatment
- (2) Promotion of anabolic effects (males and females)
- (3) Weight gain
- (4) Improvement of strength
- (5) Protection against thyroid crisis from administration of desiccated thyroid
- (6) Primary or secondary sex characters may progress
- (7) Spermatogenesis may occur¹⁵ 3

b Dosage

- (1) Oral or sublingual—methyltestosterone 15 to 30 mg daily
- (2) Intramuscular — testosterone propionate, 50 to 150 mg weekly
- (3) Pellets—testosterone, 150 to 300 mg every 2 to 4 months

c Results

- (1) General improvement in
 - (a) Strength
 - (b) Energy
- (2) Partial regrowth of hair (in order of appearance)
 - (a) Beard
 - (b) Axillary
 - (c) Pubic
 - (d) Body

3 Desoxycorticosterone acetate (DOCA) (synthetic)² 41 51 112 113

a Indications

- (1) Hypotension
- (2) Asthenia
- (3) To improve metabolism of
 - (a) Salt
 - (b) Chloride
 - (c) Carbohydrate (possibly)

b Dosage—pellets 150 mg until absorbed may last for 6 to 15 months

c Results

- (1) Generally better
- (2) Weight gain
- (3) Blood pressure increases

d Treatment of overdosage (see 40 XVI D)

(1) Remove pellets if necessary

- (2) Ammonium chloride (enteric coated)—oral 60 to 90 gr daily
- (3) Potassium citrate (20% solution)—oral, 4 to 8 cc in fruit juice daily

4 Thyroid (desiccated, USP)¹³ 15 3 11

a Indication—advisable only after a month or so of treatment with

- (1) Desoxycorticosterone
- (2) Testosterone

b Dosage—oral 1 to 2 gr daily

c Results

- (1) Most effective with evidence of pituitary myxedema
- (2) Some patients may not tolerate drug

5 Cortisone

a Indications

- (1) Supplement to above program
- (2) As sole therapy

b Dosage oral—10 to 25 mg /24 hrs

c Results

- (1) As for ACTH (see below)
- (2) Cessation of therapy not followed by sudden relapse

6 Adrenocorticotrophic hormone⁴¹ 41 104

a Indication—trial worth while because of possible stimulation of natural adrenocortical factors

b Dosage—parenteral (see 106 III E 7)

- (1) Initial—40 mg daily increase to effective dosage
- (2) Maintenance — by trial and error
- (3) Testosterone should be administered simultaneously

c Results

- (1) Well being returns
- (2) Mental improvement
- (3) Appetite stimulated
- (4) Weight increased
- (5) Breasts develop (female)

7 Gonadotropins

a Indications

- (1) Rarely if ever necessary
- (2) Preferably used after
 - (a) Testosterone
 - (b) Desoxycorticosterone

b Dosage—parenteral

- (1) Choriionic gonadotropin—500 to 1 000 ru daily¹⁵ 60 67 116

- (2) Anterior lobe gonadotropins—
100 to 300 r.u. daily^{1 4 5 8 17}
18 30 31 39 42 ■ 41 66-68 77 78
90 116 117

c Results^{5 17 23 ■ 7 76 79 81 116}

- (1) Most effective when combined
(chorionic and anterior lobe
gonadotropins⁴³)
(2) Value questionable in females
(3) Stimulation of testes to testos-
terone production is possible
(see Protocol 5 I\)

8 Estrogens⁹⁹

a Indications—amenorrhea

b Dosage

(1) Oral

(a) Stilbestrol—0.5 to 1.5 mg
daily

(b) Estrone sulfate—0.3 to 1.2
mg daily

(c) Other preparations in com-
parable dosage

(2) Parenteral—estradiol benzoate
10,000 to 50,000 I.U. weekly

c Results

- (1) Questionable value
(2) Production of periodic men-
strual bleeding possible (see 61
II E 4 for use of progesterone)

9 Adrenalin

a Indications

- (1) Hypoglycemic shock
(2) Adjunct to other therapy in
acute crisis
(3) Rarely necessary

b Dosage—subcutaneous 0.5 to 1 cc
as indicated

c Result—helpful in some

10 Protein hydrolysate or amino acids

a Indications

- (1) Protein intake decreased
(2) Severe cachexia

b Dosage—up to equivalent of 70 Gm
of protein daily

■ Results

- (1) Utilization may be inadequate
but more likely than from in-
gested proteins
(2) Other therapy may enhance
their effects

11 Glucose

■ Indications

- (1) Acute crisis
(2) Hypoglycemic shock

b Dosage—intravenous, 5 to 10 per
cent solution in saline

c Results—may be very beneficial

d Caution—severe hypoglycemia may
follow

12 Salt

a Indications

(1) As an adjunct to desoxycorti-
costerone (DOCA), but rarely
necessary

(2) Intravenously in acute crisis
but not often required

b Dosage

(1) Oral—3 to 6 Gm daily

(2) Intravenous—2,000 cc physio-
logic saline with 5 per cent
glucose

c Results

(1) Doubtful

(2) Possible edema from overdosage

13 Diet

a Hypoglycemic shock may be pre-
vented by

- (1) High protein intake
(2) Decreased carbohydrates

b Feedings—frequent

c Vitamin content—high

d Caloric intake—3,200

■ Potassium foods—theoretically low

C SUMMARY

1 General therapy

a Hypoglycemic shock

- (1) Adrenalin
(2) Glucose in saline (intravenous)

b Acute adrenal insufficiency

- (1) Adrenocortical hormone
(2) Cortisone
(3) Desoxycorticosterone acetate
(DOCA)
(4) Glucose in saline (intravenous)

c Chronic cachexia

- (1) Testosterone
(2) Desoxycorticosterone acetate
(DOCA)
(3) Thyroid
(4) Cortisone
(5) Adrenocorticotropin
(6) Adequate salt intake
(7) Other therapy

2 Results from hormonal therapy

■ General improvement when

- (1) Infection (severe) does not com-
plicate problem

- (2) Tumor is not
 - (a) Progressing
 - (b) Inaccessible
- b Successful maintenance in moderately deficient cases
- c Correction of the following in various degrees
 - (1) Anemia
 - (2) Fatigability
 - (3) Metabolic rate
- 3 Comment
 - a Therapy with testosterone desoxy corticosterone and desiccated thyroid is now relatively inexpensive
 - b After treatment over a period of a year or so some cases may get along on surprisingly little therapy¹³

XVII PROGNOSIS

A FACTORS

1 Etiology

- 2 Response to therapy
- II OUTLOOK
 - 1 In past—poor
 - 2 Present age—favorable
- C TYPE OF CASE
 - 1 Acute—death within a few months unless adequate therapy
 - 2 Chronic^{10 30 81 100}
 - a Incidence—more common
 - b Range—11 to 44 years (untreated)
 - 3 Sheehan's disease¹⁰
 - a Spontaneous recovery reported
 - b Subsequent pregnancy (if possible) believed by Sheehan to stimulate regeneration of pituitary

XVIII CAUSES OF DEATH

- A TUBERCULOSIS
- B COMA (adrenal hypoglycemia)
- C BRONCHOPNEUMONIA (terminal)

SIMMONDS DISEASE ASSOCIATED WITH PITUITARY TUMOR

Family history Tuberculosis cardiovascular disease

Past medical Normal until 30 years old

Chief complaint Tires very easily

History of present illness Amenorrhea fatigability and weakness for 18 years Fifteen years ago diagnosis of pernicious anemia Liver and iron given the latter for 10 years without benefit External strabismus developed 14 years ago Anorexia Hair has become dry and falls out Voice has changed Cold sensitivity for 5 years Mental sluggishness Thyroid 1 gr every other day About a year preceding admission pains and numbness occurred in her feet and legs She was unable to walk for 4 days

Physical examination Age 48 female single Weight 102 lbs Height 52½ in Pulse 96 BP 132/82 Skin pale yellowish tinge dry coarse Hair not remarkable Eyes puffy left external strabismus Normal visual acuity and fields Husky voice Cold hands and feet Slow movements Hypoactive reflexes

Laboratory data Urine albumin 1 plus RBC 4 280 000 Hgb 11.8 Gm (84%) WBC 8 700 Differential polymorphonuclears 76% lymphocytes 17% monocytes 6% eosinophils 1% Blood sugar 80 mg %

PROTOCOL VI FIG 51

NPV 28 mg % Plasma cholesterol 191 mg % Serum phosphorus 3.8 mg % Water test positive Sedimentation rate 50 mm/hr EKG left axis deviation 17 keto steroids 1.0 mg/24 hrs (500 cc)

Röntgenographic findings Skull—lateral area of sella turcica measures 344 sq mm on left and 228 sq mm on right thinning of dorsum sellae and depression of floor into sphenoid sinuses anterior clinoids are intact but right anterior clinoid appears elevated Chest—some fibrosis and thickened pleura in both apical regions lungs and heart normal

Treatment Desoxycorticosterone (DOCA) 1 pellet (75 mg) Testosterone 2 pellets (75 mg each) Thyroid (desiccated USP) ¼ gr daily then increased to ½ gr daily for 2 weeks 1 gr daily next 2 weeks Frequent meals of low carbohydrate and high protein Salt liberally

Progress notes Improved a great deal in 3 months Weight 108 lbs Pulse 80 BP 130/80 Thyroid 1 gr daily Desoxycorticosterone and testosterone pellets still present
Comment Hypopituitarism due to pituitary tumor which because of the weight loss and marked asthenia may be diagnosed Sim

monds' disease This case also illustrates one of the causes of obscure and resistant anemia for which the patient had 15 years of treatment Although the sella was enlarged, no visual field defects were noted External strabismus undoubtedly due to

pressure on the sixth nerve Response to hormonal therapy was excellent Patient's improvement maintained during the following 2 years Roentgen therapy and possibly surgery at later date were advised No follow up

SHEEHAN'S DISEASE

Family history Irrelevant

Past medical Negative

Chief complaint Mental depression

History of present illness At age of 31, after her youngest child was born, patient had a severe postpartum hemorrhage with shock and unconsciousness Since that time she became progressively weak and tired, her menstrual periods never returned, and all body and sexual hair disappeared Treated for anemia Given thyroid periodically Hips became stiff and her gait was awkward No hot flashes

Physical examination Age 67, female married Weight 84 lbs Height 54 in Pulse 96 BP 115/70 Marked pallor Skin dry and cold Motions and speech slow Practically no abduction of hips and only 5° to 10° adduction

Laboratory data RBC 4 340 000 Hgb 12.4 Gm WBC 8 000 Fasting blood sugar 98 mg % Plasma cholesterol 281 mg % Adrenal water test positive Sedimentation rate 54 mm/hr BMR minus 25% EKG showed inverted T T₃ 17 ketosteroids 4.5 mg/24 hrs

Roentgenographic findings Skull—calcification in right frontal region above anterior

PROTOCOL VII Figs 52-54

clinoid process Sella—normal in size Pelvis—advanced degenerative arthritis of hip joints and lower spine Ischial bursitis

Treatment and progress Three pellets (225 mg) of testosterone propionate and 1 pellet (75 mg) of desoxycorticosterone (DOCA) implanted

MONTHS

1 Thyroid (desiccated, USP) 1 gr orally daily

9 Weight 90 lbs BP went to 160/90 Regrowth of pubic hair and increase in body hair Patient comparatively well

11 Patient began to lose weight down to 83 lbs Anorexia and weakness BP 110/80 Total eosinophil count 380/cu mm 150 mg each of testosterone and desoxycorticosterone pellets implanted Improvement in 10 days

Comment A case of Sheehan's or Simmonds' disease with disability for 36 years, successfully treated with testosterone desoxycorticosterone and thyroid It is of special interest to note the development of hypertrophic arthritis in panhypopituitarism Cortisone 12½ mg/24 hrs, has since been additionally helpful in this case

ANOREXIA NERVOSA

Family history Negative

Past medical Negative

Chief complaint Loss of weight and energy

History of present illness Many emotional conflicts Believed that hips and feet were enlarging and that weight reduction was imperative Usual weight 130 lbs Reduced food intake, forced herself to vomit used cathartics and punctured nasal septum believing these would hasten weight loss Periods scanty, then amenorrhea past 2 months Patient wished to gain weight without hips enlarging (conflict)

PROTOCOL VIII Fig 55

Physical examination Age 19, female single Weight 69 lbs Height 61 in Pulse 44 BP 70 systolic indefinite diastolic Temperature 96 Looked older than her age Gaunt expression Skin dry coarse cold Axillary and pubic hair present No pigmentation present

Laboratory data Urine negative RBC 3 600 000 Hgb 84% WBC 6 350 Adrenal water test negative Sedimentation rate 2 mm/hr Urinary hormones FSH negative (unconcentrated) pregnandiol negative 17 ketosteroids 4.6 mg/24 hrs

Roentgenographic findings Skull normal
Lungs clear

Progress With psychiatric treatment and adequate diet, patient gained 25 lbs in 11 months. Menses returned. Mental problems resolved. Enjoyed good health.

Comment Amenorrhea, weight loss and low

17 ketosteroids suggest possibility of hypopituitarism; however, there was no loss of sexual hair, the adrenal water test was normal and with an adequate diet normal health was restored. Some deficiency of pituitary function may have existed as result of starvation.

SIMMONDS DISEASE²⁸

Family history Brother 72 in, father 69 in; all his sisters are 'till (one is 63 in.)

Past medical Asthma

Chief complaint Gland trouble

History of present illness Normal growth and development up to 16 or 17 years of age; none since. Sluggish and tires easily. No beard. Skin dry. Voice remained puerile. Semisoft erections. Partial loss of libido. Testosterone injections 1 year before admission. 50 mg a week for 3 months. Sexual hair appeared for first time, and penis became larger. Sexual desires increased some success at intercourse.

Physical examination Age 43; male; married (at age 35). Weight 143 lbs. Height 60¼ in. Span 67 in. Pulse 56. BP 120/80. Well developed and nourished; very youthful as in early twenties. Voice puerile. Skin smooth; fine dry. Scalp hair fine and thin. Beard absent. Fine fuzz on chest. Scant axillary and pubic hair. Testes and penis adolescent size. Prostate very small.

Laboratory data Urine normal. RBC 4,150,000. Hgb 12.4 Gm. WBC 4,100. Differential polymorphonuclears 47.5%, lymphocytes 40%, monocytes 6%, eosinophils 7.5%. Plasma cholesterol 264 mg %. BMR minus 23%. Urinary hormones: FSH negative (unconcentrated) and 17 ketosteroids 3.6 mg/24 hrs. No sperm seen in ejaculate.

Roentgenographic findings Bone age 16 years. Degenerative arthritis of cervical spine. Normal sella area 67 sq mm.

MONTHS

Up to Chorionic gonadotropin (self administered)—1,000 units 5 days a week for 34 months with an occasional lapse of several weeks. Methyltestosterone—10 to 20 mg daily for 34 months discontinued at times to test effectiveness of chorionic gonadotropin. Desiccated thyroid—½ gr during last 24 months.

PROTOCOL IX Figs 56-57

of above period. 17 ketosteroids at 28 months—3.2 mg/24 hrs. at 31 months—4.0 mg/24 hrs. Urinary FSH at 28 months positive (on APL). Increase of all sexual hair. Penile erections and libido. More endurance. No sperm in semen specimen at 30th and 34th months.

34 to Methyltestosterone, 10 mg daily.

39 Height 60¼ in. Shaves every other day. Testes larger. Wife became pregnant. Adrenal water test positive. Urinary FSH negative. 17 ketosteroids at 37th month 3.6 mg/24 hrs. Total sperm count 50,000,000. Lively and appeared fairly normal. Radial epiphyses closed.

44 Total sperm count 90,000,000. 90% motile. 30% normal morphology. 50% minor defects. Remainder markedly abnormal. Testosterone pellets 150 mg. No thyroid given.

47 Semen specimen 850,000 sperm/cc. 10% motile, large round heads in 90%. Wife had a normal boy. Patient still takes methyltestosterone 10 mg daily and desiccated thyroid ½ gr daily.

65 On 15 mg methyltestosterone daily. Total sperm count was 112 million. Majority of nonmotile forms were abnormal including wry necks, double collars, pinheads, large and small round heads. 25% motile (condom specimen). No desiccated thyroid for 5 weeks. Plasma cholesterol 316 mg %. BMR minus 20%. Total eosinophil count 343/cu mm. Excellent health.

Comment This case illustrates midpuberal hypopituitarism in a 43-year-old man beginning about 15 to 16 years of age. Therapy with chorionic gonadotropin, methyl

testosterone and desiccated thyroid produced return of normal libido potentia and spermatogenesis. Successful impregnation of wife and delivery of a normal baby. Adrenal water test positive, yet general

strength and endurance excellent 17 ketosteroids always low. Chorionic gonadotropin did not increase the 17 ketosteroid output in spite of its apparent effect on hair growth and erections

SHEEHAN'S DISEASE

Protocol X Fir 58

Family history Cardiovascular disease and stomach ulcers

Past medical Essentially negative Married 8 years One child 7 years old second 4 years old third pregnancy a miscarriage

Chief complaint Asthenia and anorexia for 6 months

History of present illness Patient became pregnant 9 months before admission and had a threatened abortion in the third month. After a hard labor she had a still birth and a severe postpartum hemorrhage requiring ten transfusions. Vomited constantly. Her skin peeled. Since that time marked fatigue dyspnea on exertion low back pain, falling hair difficulty in swallowing, anorexia and weight loss of 17 lbs. Bleeding piles occasionally. Amenorrhea for 8 months.

Physical examination Age 32 years, female married Weight 118 lbs BP 116/80 Pulse 80 Well developed and nourished Appeared prematurely old Skin dry smooth Marked pallor Axillary and pubic hair practically gone Gaping vaginal introitus with perineal scar Cervix and uterus atrophic Anal orifice scarred and contracted

Laboratory data Urine normal RBC 3,130,000 Hgb 10.4 Gm (74%) WBC 5,250 Hematocrit 29% Blood sugar 88 mg % (3 hrs after eating) Total protein 7.5 Gm % Plasma cholesterol 124 mg % Blood sodium 141.5 mEq/l Serum potassium 15.9 mg % Serum phosphorus 4.5 mg % Blood iodine (total) 5.8 micrograms % Glucose tolerance test (blood sugar mg %) fasting specimen 97 ½ hr, 105 2 hrs 86 3 hrs 95 no glycosuria Water test part 1—positive part 2—“A” factor 7.3 (positive) BMR minus 31%

Roentgenographic findings Skull—lateral area of sella measures 74 sq mm Chest negative

Treatment Testosterone 2 pellets (75 mg each) Desoxycorticosterone (DOCA), 2 pellets (75 mg each) Thyroid (desiccated USP), 1 gr daily after 1 month Ferrous sulfate 15 gr daily

Progress notes

WEEKS

6 Appetite has improved Hair starting to grow on pubis RBC 3,510,000 No change in Hgb or WBC Differential polymorphonuclears 54%, lymphocytes 34% monocytes 6%, eosinophils 2%, basophils 2% Patient went into shock while awaiting basal metabolism test Given intravenous glucose and revived BMR minus 3% Admitted to hospital for dilatation of the anal stricture

14 Much better and can go shopping now Hair growing Weight 110¼ lbs RBC 3,900,000 Hgb 11.4 Gm (82%) Testosterone 2 pellets (75 mg each) desoxycorticosterone 2 pellets (75 mg each) thyroid 1 gr daily fessol, 15 gr daily

20 Improving Pubic and axillary hair increased Constipated Weight 115 lbs BP 140/110 RBC 3,730,000 Hgb 11.8 Gm (84%) Blood sugar 102 mg %/(4 hrs after eating) Plasma cholesterol 136 mg % Roentgenogram of chest—lungs clear heart larger than on previous examination (117 cm to 123 cm) Additional therapy stilbesterol 0.5 mg orally daily

28 One day of vaginal bleeding Severe sore throat treated successfully with penicillin RBC 3,640,000 Hgb 11.2 Gm (80%) Testosterone 2 pellets (75 mg each) Desoxycorticosterone, 2 pellets (75 mg each) Thyroid, 1 gr daily

40 Vomits occasionally Head pains Fatigued sometimes Slight vaginal flow for 1 day every month with stil

- bestrol No change in blood counts or treatment
- 52 Bad head cold and influenza Hoarse More pubic hair and lanugo over entire body Intense dislike for meat and eggs Weight 118 lbs Thyroid pills stopped Pulse 62 BP 100/90 lying down, could not be recorded while standing Temperature 97° No change in blood counts Serum phosphorus 2.8 mg % Plasma cholesterol 269 mg % Testosterone, 2 pellets (75 mg each) Desoxycorticosterone 2 pellets (75 mg each) To take daily thyroid 2 gr feosol 15 gr stilbestrol, 0.5 mg orally benzedrine 5 mg essessamide 6 teaspoonfuls
- 64 Much stronger No catamenia or libido Stilbestrol stopped Pubic hair increased and new axillary hair appeared Not sleepy Weight 118 lbs Pulse 64 After resting BP 140/150/100 Temp

perature 97.6° RBC 4 000 000 Hgb 11.2 Gm Eosinophils 4.5% Plasma cholesterol 123 mg % Testosterone, 2 pellets (75 mg each) Desoxycorticosterone, 1 pellet (75 mg) All other medication discontinued

76 Color better More pubic hair Gained to 130 lbs Fingers became swollen after omitting thyroid Present weight 123 lbs BP 130/100 Hgb 11.2 Gm (80%) Plasma cholesterol 121 mg % Thyroid 1 gr daily

Comment Classical symptoms and physical signs of Simmonds disease following post partum hemorrhage She had amenorrhea loss of pubic, axillary and body hair, anorexia weight loss weakness hypoglycemic coma, anemua and a low BMR without myxedema Response to treatment very satisfactory Cortisone 15 mg daily has greatly helped this patient

REFERENCES

- 1 Aldrich C A and Walsh J A Cushing's hypophysectomy (Simmonds disease), report of case in adolescent girl J Pediatr 7 491 494 (Oct) 1935
- 2 Alpers B J Diagnosis and treatment of pituitary tumors M Clin North America 26 1679 1696 (Nov) 1942
- 3 de la Balze F A Resenstem E C Jr and Albright F Differential blood counts in certain adrenal cortical disorders (Cushing's syndrome Addison's disease and panhypopituitarism) J Clin Endocrinol 6 312-319 (Apr) 1946
- 4 Bhatia H B Cushing's hypophysectomy (Simmonds disease) describing case cured under treatment Indian M Gaz 76 259 262 (May) 1941
- 5 Brougher J C Pituitary cushing's report of patient treated with anterior pituitary extract (Simmonds disease) Endocrinology 17 128 132 (Mar Apr) 1933
- 6 Bulger H A and Barr D F Metabolic studies of pituitary insufficiency Endocrinology 20 137 148 (Mar) 1936
- 7 Calder H M Anterior pituitary insufficiency (Simmonds disease) Bull Johns Hopkins Hosp 50 87 114 (Feb) 1932
- 8 — Pituitary cushing's (Simmonds disease) treated with anterior pituitary extract J.A.M.A. 98 314 315 (Jan) 1932
- 9 Cantor M M The treatment of Simmonds disease with male sex hormones Canada M A J 52 275 277 (Mar) 1945
- 10 Collip J B Corticotrophic (adrenotropic) thyrotrophic and parathyrotrophic factors J.A.M.A. 115 2073 2079 (Dec) 1940
- 11 Colwell A R. The relation of the hypophysis to diabetes mellitus Medicine 11 139 (Feb) 1927
- 12 Cooke R T Simmonds disease due to post partum necrosis of anterior pituitary carcinoma of stomach Brit M J 2 493 494 (Oct) 1945
- 13 Cumings J N Creatine metabolism in relation to pituitary tumours Brain 67 265 269 (Sept) 1944
- 14 Cunningham J F Obstetric shock and pituitary ischaemia Irish J Med Sci 270 268 270 (June) 1948
- 15 Darley W Gordon R W and Neuburger A T Simmonds disease with therapeutic response to hormone therapy for 4 years report of case with necropsy findings Ann Int Med 21 890-902 (Nov) 1944
- 16 Daughaday W H Jaffe H and Williams R H Adrenal cortical hormone excretion in endocrine and nonendocrine disease as measured by chemical assay J Clin Endocrinol 8 244 256 (Mar) 1948
- 17 Dick G F and Dune W C Pituitary extract in Simmonds disease Endocrinology 22 703 706 (June) 1938
- 18 Doane J C Blumberg N., and Teplick E Simmonds cushing's Endocrinology 27 766 775 (Nov) 1940
- 19 Domach I and Walker A H C Combined anterior pituitary necrosis and bilateral cortical necrosis of the kidneys following concealed accidental hemorrhage J Obst Gynec Brit. Emp 53 140-147 (Apr) 1946
- 20 Dott V M Bailey P and Cushing H Hypophyseal adenomata Brit J Surg 13 314 366 (Oct) 1925
- 21 Effemann G and Muller Jag r F Über das Auftreten von Hypophysenvorderlappen Insuffizienzen nach starken Post partum Blutungen Arch f Gynak 168 867 872 (May) 1939

- 22 Escamilla R F Diagnostic significance of urinary hormonal assays: report of experience with measurements of 17 ketosteroids and follicle stimulating hormone in the urine *Ann Int Med* 10 249 290 (Feb.) 1949
- 23 Escamilla R F and Lasser H Simmonds disease (hypophyseal cachexia): clinical report of several cases with discussion of diagnosis and treatment *California & West Med* 48 343 348 (May) 1938
- 24 — Testosterone therapy in male case of hypophyseal cachexia (Simmonds disease) *Clinics* 1 710 716 (Oct.) 1942
- 25 — Simmonds disease: clinical study with review of literature: differentiation from anorexia nervosa by statistical analysis of 595 cases 101 of which were proved pathologically *J Clin Endocrinol* 2 65 96 (Feb.) 1942
- 26 Falta W Function of suprarenal cortex *Wien klin Wchnschr* 38 1203 1206 (Nov.) 1925
- 27 Farber J W Simmonds disease (pituitary cachexia): report of case *Ann Int Med* 13 2171 2177 (May) 1940
- 28 Farquharson R F and Graham H Cases of Simmonds disease *Tr A Am Physicians* 46 150 161 1931
- 29 Feldman F Roberts J H Suselman S and Lipetz B Coincidence of diabetes mellitus and hypopituitarism *Arch Int Med* 79 322 332 (Mar.) 1947
- 30 Foster M A and McCarter J C Hypopituitarism: Simmonds disease associated with pernicious anemia with bioassay of large chromophobe adenoma *J Clin Endocrinol* 1 436 441 (May) 1941
- 31 Fraser R W Forbes A P Albright F Sulikowitch H and Reifstein E C Colorimetric assay of 17 ketosteroids in urine: survey of use of this test in endocrine investigation: diagnosis and therapy *J Clin Endocrinol* 1 234 256 (Mar.) 1941
- 32 Fraser R and Smith P H Simmonds disease or panhypopituitarism (anterior): its clinical diagnosis by combined use of 2 objective tests *Quart J Med* 13 297 330 (Oct.) 1941
- 33 Friedgood H B Chemistry & Physiology of Hormones p 156 Washington D C Am Assn Advancement Sc 1944
- 34 Fulton M N and Cushing H The specific dynamic action of protein in patients with pituitary disease *Arch Int Med* 50 649 667 (Nov.) 1932
- 35 Glass S J Case of probable panhypopituitarism following post partum pituitary necrosis *J Clin Endocrinol* 4 273 276 (June) 1944
- 36 Glass S J and Davis D S Granuloma of pituitary associated with panhypopituitarism *J Clin Endocrinol* 4 489-492 (Oct.) 1944
- 37 Greene J A Alteration of carbohydrate metabolism in hypopituitarism in man *Federal Proceedings* 6 Part 2 March 1947 p 115
- 38 Gunther L and Courville C B Hypophyseal cachexia (Simmonds disease) with atrophy of anterior lobe of pituitary gland: report of case *J Nerv & Ment Dis* 82 40 56 (July) 1935
- 39 Hawkinson L F Simmonds disease (pituitary cachexia): report of case in which patient responded to anterior pituitary like principle of pregnancy urine *JAMA* 105 20 23 (July) 1935
- 40 Hemphill R E and Reiss M Corticotrophic hormone in the treatment of involutional melancholia with hypopituitarism and pituitary cachexia *J Ment Sc* 88 559 565 (Oct.) 1942
- 41 — Pituitary cachexia treated with corticotrophic hormone *Brit Med J* 2 211 213 (Aug) 1944
- 42 Hicks C S and Hone F S Pituitary cachexia with disturbance of circulatory regulation: Result of treatment with prolactin *Proc Roy Soc Med* 28 925 932 (May) 1935
- 43 Horrax H Hursthal L M Hare H F and Younghusband O Unpublished data
- 44 Hursthal L M Unpublished data
- 45 Hursthal L M Bruns H J and Musulin N Development of spermatogenesis in hypogonadism *J Clin Endocrinol* 9 1245 1258 (Dec.) 1949
- 46 Hursthal L M and Younghusband O Diagnosis of chromophobe pituitary tumor (presumed or verified) *Radiology* 11 19 185 (Feb.) 1949
- 47 Ingraham F H and Scott H W Cranio-pharyngiomas in children *J Pediat* 29 95 116 (July) 1946
- 48 Israel I L Diagnosis and treatment of amenorrhea *M Clin North America* 26 1831 1855 (Nov.) 1942
- 49 Jailer J W A fluorometric method for the clinical determination of estrone and estradiol *J Clin Endocrinol* 1 564 579 (July) 1948
- 50 John H J The possible relationship between acromegaly and diabetes with a report of three cases *Arch Int Med* 37 489 511 (Apr.) 1926
- 51 Kalk H Zur Frage der Beziehung zwischen Hypophysenvorderlappen und Nebennierenrinde *Deutsche med Wchnschr* 60 893 894 (June) 1934
- 52 Kinsel L W Spermatogenesis in a panhypopituitary eunuchoid as the result of testosterone therapy *J Clin Endocrinol* 7 781 786 (Dec.) 1947
- 53 Kirschbaum J D and Levy H A Tuberculoma of hypophysis with insufficiency of anterior lobe: clinical and pathological study of 2 cases *Arch Int Med* 68 1095 1104 (Dec.) 1941
- 54 Klinefelter H F Jr Albright F and Gruenewald G C Experience with quantitative test for normal or decreased amounts of follicle stimulating hormone in urine in endocrinological diagnosis *J Clin Endocrinol* 3 529 544 (Oct.) 1943
- 55 Kunststadter R H Pituitary emaciation (von Bergmann) *Endocrinology* 22 605 612 (May) 1938
- 56 Jeffcoate T N A Postpartum necrosis of pituitary *Int J Med Sc* 270 256 264 (June) 1948
- 57 Laub G R Simmonds disease in old age *South Med & Surg* 102 56 58 (Feb.) 1940
- 58 Lasser H and Curtis L E Treatment of post-traumatic Simmonds disease with methyl testosterone linguet *J Clin Endocrinol* 5 363 366 (Nov.) 1945
- 59 Louw J T Post partum necrosis of the anterior lobe of the pituitary body *Clin Proc* 6 361 367 (Nov.) 1947
- 60 Macy J W Claiborne T S and Hursthal L M The circulation rate in relation to metabolism in thyroid and pituitary states (Decholin Method) *J Clin Investigation* 15 37 40 (Jan.) 1936

- 61 Maranon C and Morros J Pituitrin hyperglycemia and its possible value in diagnosis *Endocrinology* 13 564 572 (Nov-Dec) 1929
- 62 Marti T Zur Hypophysen-entplantation bei Morbus Simmonds *Schweiz med Wchnschr* 72 38 40 (Jan) 1942
- 63 Marx H Störungen des Wa. erhaltens bei Erkrankungen der Hypophyse *Deutsche med Wchnschr* 53 593 (Apr) 1927
- 64 McGovern B F Somnolence associated with pituitary cachexia: case report of patient who responded to pituitary treatment *Endocrinology* 16 40 406 (July-Aug) 1937
- 65 Meyer W C Untersuchungen und Beobachtungen an Fällen von hypophysärer Magerkeit (Simmonds) und deren Behandlung insbesondere durch Hypophysenimplantation *Deutsches Arch f Klin Med* 182 351 368 (July) 1938
- 66 Mogensen E Simmonds syndrome Review *Acta med Scandinav* 105 360 377 1940
- 67 — Three cases of Simmonds syndrome With special reference to clinical diagnosis and hormone treatment *Acta med Scandinav* 105 378 394 1940
- 68 — Spontaneous hypoglycemia in Simmonds disease *Endocrinology* 27 194 199 (Aug) 1940
- 69 Mo E F Simmonds disease: report of 2 cases caused by intracranial tumors *J Clin Endocrinol* 2 395-40 (June) 1942
- 70 Mulino M B and Pomerantz L Pituitary replacement therapy in pseudo hypophysectomy *Endocrinology* 29 558 563 (Oct) 1941
- 71 Nelson E W and Michaels J P Acute post partum necrosis of anterior hypophysis *Am J Obst & Gynec* 58 817 825 (May) 1946
- 72 Novak E Anterior pituitary and anterior pituitary like substances: therapeutic applications *JAMA* 104 998 1002 (Mar) 1935
- 73 Ornstein E A Management of primary amenorrhea in hypopituitarism *J Clin Endocrinol* 1 899 904 (Nov) 1941
- 74 Paschki K E Cantarow A and Rakoff A E Studies in cases of pituitary tumors *J Clin Endocrinol* 7 466-467 (June) 1947
- 75 Peters J P German W J and Man E B Serum precipitable iodine in pituitary disease *J Clin Endocrinol* 9 1292 1313 (Dec) 1949
- 76 Plummer D E and Jaepfer J R Pituitary cachexia (Simmonds disease): report of case with autopsy *Arch Neurol & Psychiat* 40 1013 1018 (Nov) 1938
- 77 Rau L Pituitary cachexia (Simmonds disease) treated with anterior lobe extract *Lancet* 1 1502 (June) 1935
- 78 Rea C and Hoover W A Simmonds disease with case report *Pennsylvania M J* 42 27 30 (Oct) 1938
- 79 Regester R F and Cuttle T D Cachexia hypophyseopriva (Simmonds disease) *Endocrinology* 21 558 560 (July) 1937
- 80 Reiche F Zur Kenntnis der Simmondschen Krankheit *Med Klin* 26 1447 1448 (Sept) 1930
- 81 Reifstein E C Jr Conference on Metabolic Aspects of Convalescence Including Bone & Wound Healing Symposium on Urinary Corticosteroids 10th Meeting June 15 16 New York Josiah Macy Jr Foundation 1945 pp 131 219
- 82 Richardson H B Simmonds disease and anorexia nervosa *Arch Int Med* 63 1 28 (Jan) 1939
- 83 Rochat R L Maladie de Simmonds—aménorrhée et greffe hypophysaire foetale *Helvet med acta* 9 373 376 (July) 1942
- 84 Siler W T *Endocrine Function of Iodine* p 126 Cambridge Harvard University Press, 1940
- 85 Schenker V and Browne J S Protein Anabolic Activity of Steroid Compounds (Reifen F C) 1942 p 45
- 86 Segaloff A Testicular dysfunction: Diagnosis and treatment *Am Pract* 1 15 22 (Sept) 1946
- 87 Sheehan H L Simmonds disease due to post partum necrosis of anterior pituitary *Quart J Med* 277 309 (Oct) 1939
- 88 Sheehan H L and Summets V A The syndrome of hypopituitarism *Quart J Med* 18 319 378 (Oct) 1949
- 89 Silver S Simmonds disease (cachexia hypophyseopriva): report of case with post mortem observations and review of literature *Arch Int Med* 51 175 197 (Feb) 1933
- 90 Simmonds M Ueber Hypophysenschwund mit tödlichem Ausgang *Deutsche med Wchnschr* 40 322 (Feb) 1914
- 91 Simmonds M Atrophie des Hypophysenorderlappens und hypophysäre Cachexie *Deutsche med Wchnschr* 44 852 854 (Aug) 1918
- 92 Simpson H L Major Endocrine Disorders John Bale Medical Publications 1938 p 78
- 93 Snapper I Groen J Hunter D and Witts L J Achlorhydria anemia and subacute combined degeneration in pituitary and gonadal insufficiency *Quart J Med* 6 195 209 (Apr) 1937
- 94 Spain A W and Geoghegan F Diabetes insipidus with postpartum pituitary necrosis: A report of two cases *J Obst & Gynaec Brit Emp* 53 223 227 (June) 1946
- 95 Starr P and Davis I Endocrine studies of patients after subtotal hypophysectomy *Ann Surg* 113 778 790 (May) 1941
- 96 Stephens D J Chloride excretion in hypopituitarism with reference to adrenocortical function *Am J M Sc* 199 67 73 (Jan) 1940
- 97 — Pituitary and adrenocortical insufficiency: use of sodium chloride in treatment of hypopituitarism *J Clin Endocrinol* 1 109 112 (Feb) 1941
- 98 Stewart A Case of Simmonds disease *Lancet* 1 1391 1392 (Dec) 1936
- 99 Striker C A case of Simmonds Disease (Cachexia Hypophyseopriva) with recovery *JAMA* 101 1994 (Dec) 1933
- 100 Sundeman F W and Rose E Studies in serum electrolytes changes in serum and body fluids in anorexia nervosa *J Clin Endocrinol* 8 209 220 (Mar) 1948
- 101 Talbot F H Internal & Secretory System *Metabolism* Vol 13 p 84 New York Appleton 1928
- 102 Talbot N H Albright F Saltzman A H Zygmuntowicz A and Waxom R Excretion of 11-oxycorticosteroid like substances by normal and abnormal subjects *J Clin Endocrinol* 7 331 350 (May) 1947
- 103 Thorn G W The Diagnosis and Treatment of Adrenal Insufficiency p 52 Springfield Ill Thomas 1949
- 104 Thorn G W Prunty F T G and Forsham P H Clinical studies on effects of pituitary adrenocorticotrophic hormone *Tr A Am Physicians* 60 143 150 1947

- 105 Tompett E L and Oastler E G The determination of the total 17 ketosteroids in urine a simplification of the method for routine use in a hospital biochemical laboratory Glasgow M J 27 281 297 (Oct) 1946
- 106 Venning E H and Browne J B L Excretion of glycogenic corticoids and of 17 ketosteroids in various endocrine and other disorders J Clin Endocrinol 7 79 101 (Feb) 1947
- 107 von Bergmann G Magerkeit und Magersucht Deutsche med Wchnschr 60 123 126 (Jan) 1934
- 108 Wagner H Galactose tolerance test in endocrine disorders in children Am J Dis Child 65 207 234 (Feb) 1943
- 109 Weinstein A Multiglandular syndromes resembling Simmonds disease with case report Am J M Sc 189 245 253 (Feb) 1935
- 110 Werner S C and West R Nitrogen retention creatinuria and other effects of treatment of Simmonds disease with methyl testosterone J Clin Investigation 22 335 344 (May) 1943
- 111 Wilder J Ein neues hypophysares Krankheitsbild Die hypophysare Spontanhypophysektomie Deutsche Ztschr f Nervenhe 112 192 250 1930
- 112 Williams R H and Whittenberger J L Treatment of Simmonds disease J Clin Endocrinol 2 539 550 (Sept) 1947
- 113 Williams R H Whittenberger J L Bissell G W and Weinglass A R Treatment of adrenal insufficiency J Clin Endocrinol 5 163 180 (Apr) 1945
- 114 Wohl M H and Larson E Diagnosis and treatment of pituitary gland disorders M Clin North America 26 1675 1678 (Nov) 1947
- 115 Young F C Anterior pituitary gland and diabetes mellitus New England J Med 221 635 646 (Oct) 1939
- 116 Zondek H The Diseases of the Endocrine Glands ed 3 pp 291 292 New York Wood 1935
- 117 Zondek, H., and Koehler G Behandlung der hypophysar cerebralen Magersucht mit dem Hypophysenvorderlappenhormon Prolan Med Klin 28 1125 11 6 (Apr) 1932



FIG 51 (Left top) SIMMONDS DISEASE — ENLARGEMENT OF SELLA TURCICA (See Protocol 5 VI) Although patient appears to be fairly well nourished there has been weight loss (20 lbs) asthenia decrease in pubic axillary and body hair Cause — pituitary tumor without visual field changes



FIG 53 (Right top) SIMMONDS DISEASE (SHEEHAN TYPE) (See Protocol 5 VII Figs 52 54) Note that extreme emaciation is not present after 36 years of marked hypopituitarism



FIG 52 (Left bottom) SIMMONDS DISEASE (SHEEHAN TYPE) (See Protocol 5 VII Figs 53 54) Age 61 Onset of disease following severe postpartum hemorrhage at age 31



FIG 54 (Right bottom) HIP JOINTS IN SIMMONDS DISEASE (See Protocol 5 VII Figs 52 53) Hyper-tropic joint changes may occur in hypopituitarism as well as in hyperpituitarism (acromegaly)



FIG 55 ANOREXIA
NERVOSA (See Protocol
5 VIII)

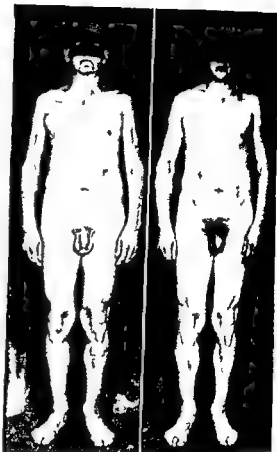


FIG 56 SIMMONDS DISEASE (See Protocol 5 IX Fig 57) Age 43 *Chief complaints* Cessation of growth at 16 years of age Never shaved no voice change moderate libido Married at 35 sexual life unsatisfactory Bone age at 43 16 years (*Left*) Condition before therapy Aspermia before treatment and after 6 months of chorionic hormone average 5 000 to 6 000 units weekly methyltestosterone 10 mg daily and thyroid (desiccated USP) $\frac{1}{2}$ gr daily (*Right*) Condition of patient after 5 months of only methyltestosterone (30 mg daily) Spermatogenesis returned with successful impregnation Total sperm count 50 000 000 Shaves every other day normal sexual function and general improvement Water test positive (Hurxthal L M Bruns H J and Musulin N Development of spermatogenesis in hypogonadism J Clin Endocrinol 9 1245)



FIG 57 SIMMONDS DISEASE (See Iro tocol 5 I\ Fig 56) Age 43 Normal development until 16 or 17. Sella turcica normal size 67 sq mm Roentgenogram of hands showing bone age of 16 years Two years after therapy radial epiphyses closed

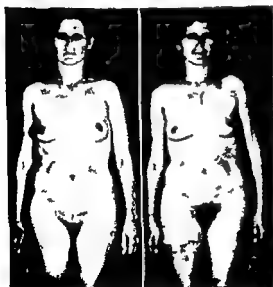


FIG 58 SIMMONDS DISEASE (SHEEHAN TYPE) (See Protocol 5 X) (Left) Two months after initiation of treatment Patient developed Simmonds disease after postpartum hemorrhage She survived rectal surgery after multihormonal therapy A slight amount of pubic hair has grown (Right) Regrowth of pubic hair Patient maintained on thyroid (desiccated USP 1 gr) testosterone and desoxycorticosterone pellets

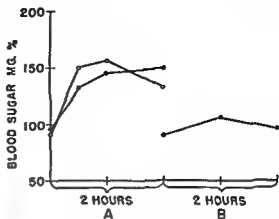


CHART 17 ORAL GLUCOSE TOLERANCE CURVE IN SIMMONDS DISEASE Age 49 female Amenorrhea since age 40 without any vasomotor symptoms Loss of axillary and pubic hair BP 120/0 Urinary hormone assays for FSH and estrin negative, 17 ketosteroids 3 mg/24 hrs Plasma cholesterol 147 mg % BMR minus 17% Desoxycorticosterone acetate and testosterone pellets implanted Plasma cholesterol rose to 357 mg % Given proloid (gr 1/2 orally) with further improvement Plasma cholesterol 200 mg % BP rose to 160/120 later leveled off to 140/100 Regrowth of pubic hair Pellets of desoxycorticosterone (150 mg) and testosterone (150 mg) implanted again after 3 months Still effective 9 months later and no complaints

(A) Glucose tolerance curves before treatment Line with hollow dots shows capillary blood line with solid dots venous blood

(B) Glucose tolerance curve 1 year later The curves are the reverse of what usually occurs A = a diabetic type and B is a low curve typical of hypopituitarism Is this the result of desoxycorticosterone acetate?

SECTION II

PITUITARY MYXEDEMA

I DEFINITION

A condition clinically indistinguishable from primary myxedema (see 25 \III), due to a predominant thyrotropic deficiency of the anterior pituitary (see Protocol 6 \I)⁴ p 11

II DIAGNOSIS

A COMMENT

- 1 The diagnosis of pituitary myxedema will increase as the number of individuals with idiopathic myxedema are subjected to roentgenograms of the skull
- 2 It is to be admitted that even without enlargement of the sella, a few cases of

idiopathic myxedema may be of pituitary origin

- 3 Tests for adrenal insufficiency are usually normal in primary thyroid myxedema, thus serving as an important differential point
- 4 It is plausible that in primary thyroid myxedema of long standing, the pituitary gland itself may become deficient due to myxedematous changes thus producing a state of panhypopituitarism, in which case tests for gonadotropic thyrotropic and adrenal cortical function would point to a primary pituitary disorder
- 5 The differences between the two types are tabulated below

	PITUITARY MYXEDEMA (Secondary)	THYROID MYXEDEMA (Primary)
B GENERAL		
Occurrence	Rare	More common
Complaints	Same	Same
Headache	Common	Not usual
Deafness	Absent	Occasionally ⁴
Angina pectoris	Not likely to be present	Likely ³
Myxedema heart	Reported	Often present
Menorrhagia	Absent	Possible ³
Amenorrhea	Usual ⁷	Found in some ⁵
Hypoglycemic shock	May occur ⁵	Absent
Appearance	Identical	Identical
Integument changes	Same	Same
Pigmentation	Absent may have freckles	May be present
Hair	Absent or very little	Decreased may be increased ⁴
Visual fields	Variable	Normal
Blood pressure	Normal or decreased may be elevated before onset ⁴ ⁸	Normal or elevated ^{4, 8}
Sensitivity to thyroid	May be marked and also invoke angina of effort	Absent or occurs very rarely except for invoking angina of effort
C LABORATORY DATA		
Blood chemical analyses		
Nonprotein nitrogen	Normal or rarely increased ³	Normal or rarely increased
Protein	Lower than for primary myxedema ³ ⁵ ⁸	Normal or increased ⁵
Cholesterol	Usually increased ³	Usually increased ³
Sodium	Decreased (maybe) ¹ ³ ⁹	Normal

	PITUITARY MYXEDEMA (Secondary)	THYROID MYXEDEMA (Primary)
Potassium	Normal or increased ³	Normal
Chlorides	Normal or decreased ^{1 3 9}	Normal
Function tests		
Glucose tolerance	Normal or increased ^{3 8 10}	Variable
Insulin tolerance	Rapid drop in level slow recovery ^{8 9}	Slow drop faster recovery ^{8 9}
Adrenal water	Positive ^{8 9}	Usually negative unless pituitary secondarily affected and deficient in ACTH (?)
Miscellaneous		
Basal metabolic rate	Low ^{8 10}	Low ³
Electrocardiogram	Normal or few changes ^{3 8}	Low voltage, flat or inverted T waves ¹
Gastric analysis	Anacidity ⁸	May have acid
Urinary hormone assays		
FSH	Negative usually ⁹	Negative or increased after menopause
17 ketosteroids	Absent or very low ^{8 9}	Low ³
Vaginal smears	Estrogen deficient ^{3 8}	May have estrogen effect
D ROENTGENOGRAPHIC FINDING		
Sella turcica	Normal or enlarged ^{1 4 8}	Normal, except in cretinism or aneurysm of internal carotid artery

III TREATMENT

A HORMONAL (see Fig 59)

- 1 The following should be used before thyroid is administered
 - a Salt—adequate intake
 - b Desoxycorticosterone acetate (DOCA)

c Testosterone

2 Thyroid (desiccated USP)

- a Dosage—oral $\frac{1}{4}$ gr daily initially then increase cautiously
- b Small doses prevent
 - (1) Adrenal insufficiency
 - (2) Coronary complications

REFERENCES

- 1 Beaumont G E and Robertson J D Pituitary hypothyroidism with impaired renal function *Brit M J* 2 356 357 (Sept) 1943
- 2 del Castillo E B Quirno N Gamban M A and Manzoli J Mixedema de origen hipofisario *Medicina* 5 416-424 (July) 1945
- 3 Clutton H E Jr Bennett W A and Kepler J J Anterior pituitary insufficiency (pan hypopituitarism—Simmonds disease) pituitary myxedema and congestive heart failure (myxedema heart): report of case and findings at necropsy *Ann Int Med* 10 732 745 (Oct) 1948
- 4 Good W H and Ellis A G A case of myxedema with tumor of pituitary body and lesions of other endocrine glands *Endocrinology* 11 431 437 1918
- 5 Hurxthal L M Unpublished data
- 6 Hurxthal L M and Musulin N Hypertrophic and myxedema *Lahey Clin Bull* 4 102 110 (Apr) 1945
- 7 Horwitz M A case of pituitary myxedema *Clin Proc* 6 396-403 (Nov) 1947
- 8 Lerman J and Stebbins H D Pituitary type of myxedema: further observations *JAMA* 119 391 395 (May) 1942
- 9 Means J H Hertz S and Lerman J Pituitary type of myxedema or Simmonds disease masquerading as myxedema *Tr A Am Physicians* 55 32 53 1940
- 10 Miller R A Pituitary hypothyroidism with with impaired renal function *Brit Med J* 11 650 651 (Nov) 1946
- 11 Wadsworth O F A case of myxoedema with atrophy of the optic nerves *Boston M & S J* 112 5 6 (Jan) 1885

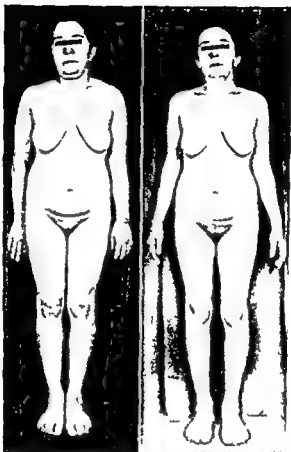


FIG 59 PITUITARY MYXEDEMA AND ADRENAL INSUFFICIENCY (See Protocol 6 \I)
(Left) Before treatment patient appeared to be typically myxedematous but history and loss of pubic and axillary hair raised question of pituitary origin Weight 136 lbs BP 96/80 Plasma cholesterol 309 mg % Electrocardiogram abnormal Adrenal water test positive Sella enlarged (Right) Nine months later after continuous therapy with thyroid testosterone and desoxycorticosterone Weight 121 lbs BP 160/100 Much improved Regrowth of axillary and pubic hair

SECTION 7

PITUITARY ADRENAL INSUFFICIENCY

(Pituitary Addison's Disease)

I DEFINITION

A condition due to a predominant deficiency of the pituitary adrenotropic hormone and characterized by all the symptoms of true Addison's disease except for the mucous membrane pigmentation and black (ink spot) freckles which are usually seen in the latter (see Protocol 7 VI to VIII)

II DIAGNOSIS

A COMMENT (see Fig 60)

- 1 Pituitary 'Addison's disease' is essentially similar to Simmonds disease
- 2 A comparison of the two conditions is made in the following section

	<i>Pituitary Adrenal Insufficiency</i>	<i>Addison's Disease</i>
B GENERAL		
Complaints	Same	More marked progressive anorexia weakness and weight loss
Diarrhea	Rare	Marked only in acute crisis
Hypoglycemic attacks	Occasionally	Common especially at time of infection
Menses	Amenorrhea usually	Normal
Appearance	Looks sick	Looks sicker
Integument		
Color	No darkening peculiar yellow	Often generalized darkening especially at exposed surfaces
Pigmentation of mucous membranes	Absent	Present usually
Vitiligo	Present	Present
Freckles (black)	Absent	Present
Hair		
Facial	Scant	Normal or decreased
Axillary	Absent	Normal or decreased
Pubic	Absent	Normal or decreased
Body	Scant	Normal
Visual fields	Variable	Normal
Blood pressure	Low, unless previous hypertension	Low unless previous hypertension
Genitalia	Variable findings, usually atrophy	Normal
C LABORATORY DATA		
Urine		
Urea	Normal or decreased	Normal or decreased
Sodium	Increased	Increased
Potassium	Normal	Decreased
Chlorides	Increased	Increased
Hematology		
Red blood cells	Normal or decreased ³	Decreased or increased (crisis)
Hemoglobin	Normal or decreased ³	Normal or increased (crisis)
White blood cells	Normal	Normal or increased (crisis)

	<i>Pituitary Adrenal Insufficiency</i>	<i>Addison's Disease</i>
Eosinophils	Increased	Increased ²
Hematocrit	Decreased usually	Decreased or increased with fluid loss
Blood chemical analyses		
Sugar	Normal or decreased	Normal or decreased (crisis)
Nonprotein nitrogen	Normal	Normal or increased (crisis or late in disease)
Protein	Normal ³ or decreased (unless simultaneous pituitary myxedema)	Normal or increased (crisis or late in disease)
Albumin	Decreased	Normal or decreased
Globulins		
Alpha	Decreased	Normal or slightly decreased
Beta	Normal or increased	Normal
Gamma	Normal or increased	Increased
Fibrinogen	Normal or increased	Normal or increased
Cholesterol	Normal or decreased ³	Normal or decreased
Sodium	Normal or decreased ³	Normal or decreased (crisis or late in disease)
Potassium	Normal ³	Normal or increased (crisis or late in disease)
Calcium	Normal ³	Normal or decreased (crisis)
Phosphorus	Normal or decreased ³	Normal or increased (crisis)
Chlorides	Decreased	Normal or decreased (crisis or late in disease)
Function tests		
Glucose tolerance	Normal or increased ³	Normal or increased
Insulin tolerance	Decreased very low curve ³	Decreased, very low curve
Adrenal water	Positive	Positive
Eosinophils	Usually delayed response	No response
Miscellaneous tests		
Basal metabolic rate	Decreased often below minus 20 per cent	Decreased, rarely below minus 20 per cent
Blood volume	Normal	Normal or decreased (crisis or late in disease)
Urinary hormone assays		
FSH	Usually negative	Normal unless malnutrition
17 ketosteroids	Absent or very low (about 0 to 2 mg/24 hrs) ^{1 2}	Absent or very low (about 2 to 4 mg/24 hrs)
D ROENTGENOGRAPHIC FINDING		
Sella turcica	Normal or enlarged	Normal

PITUITARY MYXEDEMA AND ADRENAL INSUFFICIENCY

PROTOCOL VI FIG 59

Family history Cardiovascular disease and diabetes
Past medical Married 17 years One child
Chief complaint Weakness of 2 years' duration

History of present illness Menarche at 14 years of age periods regular but scanty Sudden amenorrhea when 34 years old Hot flashes Always sensitive to cold Anorexia Nearly 2 years before entry patient was

found to have low blood pressure. Complained of weakness and fatigue. About 1½ years before admission began to have spells of vomiting occurring in the morning and associated with vague lower abdominal pain. Noted dryness of her hair and decreased perspiration. A few months later speech became slow, and voice seemed lower in pitch. Lost a great deal of her pubic, axillary and upper lip hair. Anemia discovered. Lost 22 lbs in the past year because of anorexia. Around 3 months before entry, so weak that she could not work.

Physical examination Age 41, female married. Weight 136 lbs. Height 61 in. Pulse 60. BP 96/80. Looks pale and pasty. Puffiness around face, eyes, hands, fingers and toes. Skin is dry, thick. Marked pallor of palms, nails and mucous membrane. Nails normal. Axillary hair absent, pubic, very scanty. Scalp hair is very dry, coarse. Gingivitis and pyorrhea. Speech slow and thick. Pelvic normal. Her movements are usually slow.

Laboratory data Urine normal. RBC 3,830,000. Hgb 11.5 Gm (82%). WBC 5,000. Differential: polymorphonuclears 44%, lymphocytes 28.5%, monocytes 5%, eosinophils 1.5%, basophils 3%. VpN 32 mg %. Total protein 8.3 Gm %. Albumin 4.4 Gm %. Globulin 3.9 Gm %. A/G ratio 1.1. Plasma cholesterol 309 mg %. Glucose tolerance test (blood sugar mg %) lasting 78 ½ hr: 126, 2 hrs 113, 3 hrs 85. Urinalysis negative for sugar during tolerance test. Adrenal water test positive. Bilirubin 0.2 mg %. Sedimentation rate 81 mm/hr. EKG delayed AV conduction, abnormal T2 and T4. Urinary hormones: FSH weak positive (unconcentrated), 17 ketosteroids 3.6 mg/24 hrs.

Roentgenographic findings Skull—sella appears enlarged, measures 140 sq mm, but the anterior and posterior clinoids are intact. Chest normal.

Treatment Testosterone 1 pellet (75 mg). Desoxycorticosterone 1 pellet (75 mg). Salt to be used liberally. Thyroid (desiccated, USP) 1 gr daily, 2 weeks later.

Progress and treatment

WEEKS

3 Weight 134 lbs. Pulse 78 to 80. BP

120/85. Patient looks about the same. Feels warmer. Complains of noises in head and an occasional headache. Sleeps poorly. Plasma cholesterol 245 mg %. Urinary hormones: FSH weak positive (unconcentrated), 17 ketosteroids 3.6 mg/24 hrs. Thyroid 1½ gr daily.

7 Weight 132½ lbs. Pulse 80. BP 125/84. Pubic and axillary regions show slight growth of hair. RBC 3,790,000. Hgb 11.2 Gm (80%). WBC 5,400. Differential: polymorphonuclears 45%, lymphocytes 41%, monocytes 12%, eosinophils 2%. Plasma cholesterol 175 mg %. Total protein 6.7 Gm %. Thyroid 1½ gr daily.

11 Weight 128 lbs. Pulse 80. BP 120/84. Improved. No hot flashes. RBC 4,150,000. Hgb 11.4 Gm (84%). WBC 5,000. Sedimentation rate 59 mm/hr. Thyroid 1½ gr daily.

20 Feels fine. BP 120/85. Weight 117½ lbs. Thyroid 1½ gr daily. Desoxy corticosterone 1 pellet (75 mg). Testosterone 1 pellet (75 mg).

24 Much stronger. No complaints. Pulse 80. BP 160/100. Weight 119½ lbs. RBC 4,520,000. Hgb 12.4 Gm (89%). WBC 5,000. Plasma cholesterol 132 mg %. Thyroid medication continued. Pellets still present.

48 No complaints. Working. Amenorrhea. Axillary and pubic hair maintained. BP 150/100. No pellets. Thyroid 1½ gr daily.

Comment Myxedema presumably of pituitary origin associated with weakness, anorexia, loss of axillary and pubic hair and amenorrhea at age of 34 with occurrence of hot flashes which ceased in 1 year. Low BMR and high plasma cholesterol. Positive adrenal water test. Excellent response to testosterone, desoxycorticosterone and thyroid. The finding of weak positive urinary FSH although decreased for the menopause suggests that thyrotropic and adrenocorticotrophic hormones were chiefly deficient. In long standing cases of primary myxedema it is entirely possible that pituitary deficiency may result.

PITUITARY MYXEDEMA AND ADRENAL INSUFFICIENCY

PROTOCOL VII

Family history Essentially negative*Past medical* Married 25 years Husband living and well Five children, all normal deliveries Youngest child 14 years old

YEARS BEFORE

ADMISSION

12 Cholecystectomy All teeth were removed D & C for menorrhagia Pathologic report hypertrophic endometritis

10 Diagnosis of hypothyroidism and secondary anemia

5 Permanent loss of sight in right eye after abscess of right maxillary sinus

Chief complaints Weakness, cold hands and feet for 10 years dry, thickened skin and amenorrhea for 12 years*History of present illness* Well and robust until 12 years previously, when she lost about 42 lbs Amenorrhea followed D & C Noticed absent body and scant axillary hair Nails brittle Skin dry and flaky Mentally and physically sluggish Disliked cold weather Hearing impaired Ten years before, BMR was minus 19%, remained low in spite of thyroid medication For some years, endurance and strength very poor Dyspnea, palpitation and fatigue on slight exertion Speech slow and deliberate Stomach easily upset Spells of nausea and vomiting occasionally Constipation about a year Paresthesias and coldness of her hands and feet Admitted to hospital for study*Physical examination* Age 45 female Weight 170½ lbs Height 65½ in Pulse 92 BP 165/110 Temperature 97.6° Typical appearance of myxedema Skin—pale thick, dry, scaly Extremities very cold Nails brittle Hair dry and sparse Axillary and pubic hair scant Body hair absent Paresis of right internal rectus right eye turns out and downward Right pupil is larger than the left Fundi—primary optic atrophy, retinal vessels show marked degree of sclerosis Visual fields—almost total blindness in right eye Patient can count fingers at 1 ft distance in the upper temporal field Left eye 6/6 Thyroid gland slightly enlarged and nodular Heart normal, beats forceful Lungs clear Pelvic normal Reflexes sluggish Speech slow and deliberate*Laboratory data* Urine—1 plus albumin, 40 to 50 WBC per high powered field RBC 4,310,000 Hgb 12.2 Gm (87%) WBC 4,650 Hematocrit 35% NPN 30 mg % Plasma cholesterol 408 mg % Spinal fluid dynamics and analysis normal BMR minus 35% Sedimentation rate 61 mm/hr EKG low voltage and flat T waves Gastric analysis—75° of free acid, 30 min 70°, 45 min*Roentgenographic findings* Skull—a large aneurysm of the right internal carotid artery involving the sella, partially calcified (See Fig 26) Chest—heart slightly enlarged in all its diameters lung fields clear*Treatment* Thyroid (desiccated, USP) ½ gr daily, increased to 1 gr Sodium chloride, 5 to 6 Gm (capsules) daily Feosol 2 tablets t.i.d Vitamin B complex 2 teaspoonfuls t.i.d Haliver oil, 1 capsule daily*Diagnoses* Pituitary myxedema and adrenal insufficiency third nerve palsy due to pressure of aneurysm on hypophysis and third nerve*Progress and treatment*

MONTHS

4 Well for 1 month only She suddenly became nauseated and within a few hours was comatose Regained consciousness in 3 or 4 days Given glucose and salt solution rectally at home Second admission to hospital for further study and management Urine normal RBC 4,420,000 Hgb 80% WBC 6,660 Differential polymorphonuclears 52%, lymphocytes 36%, monocytes 8%, eosinophils 2%, basophils 2% NPN 19 mg % Glucose tolerance test (blood sugar mg %) fasting, 70, ½ hr, 90 1 hr 70 2 hrs, 80 3 hrs 70 4 hrs, 60 5 hrs, 40 6 hrs 44 Salt deprivation test unsuccessful because patient became nauseated at the end of the 36th hr Blood chloride had fallen from 523 to 463 mg % during the preceding 8 hrs Blood sugar 50 mg % Prompt recovery with the use of intravenous glucose, saline and adrenal cortical ex

tract BMR minus 10% EKG essentially inversion of all T waves, rate 80
Thyroid $\frac{1}{4}$ gr daily Sodium chloride 6 to 8 Gm (capsules) daily Frequent feedings to avoid hypoglycemic attacks

5 Intervals of good health and recurrent to collapse During these attacks she had 11 anorexia, nausea, vomiting weakness and apathy BP 140 to 70 systolic Thyroid $\frac{1}{4}$ gr daily, increased to $\frac{3}{8}$ gr sometimes Sodium chloride 2 Gm (capsules) daily Precortin $\frac{1}{2}$ to 1 cc subcutaneously every second to fifth day Low-carbohydrate high fat and high protein intake with frequent feedings Multiple vitamin capsules 1 daily

36 Returned for checkup Tires rather easily Appetite variable No coma for 3 years No paresthesias Pale looks sick Weight 115 lbs Tongue smooth Dry skin Heart normal few extra systoles P_2 is greater than A Pulse 84 BP 190/100 Neurologic examination normal Optic nerve atrophy on the right left normal Urine—albumin 227 mg % few hyaline casts and WBC Hgb 12.8 Gm (91%) WBC 5700 Blood sugar 72 mg % (4 hrs after eating) NIN 38 mg % Blood urea nitrogen 13 mg % Plasma cholesterol 243 mg % Blood chloride 358 mg % Water test positive—A factor is equal to 6 PSP total 45%

Venous pressure 10 cm Sedimentation rate 44 mm/hr Chest roentgenogram—cardiothoracic measurements 13.4 to 25.6, lungs clear Thyroid, increased to $\frac{3}{4}$ gr in 1 month after blood pressure drops Sodium chloride and precortin discontinued

39 Feels much better Less fatigue Does her own housework Color good Skin soft BP 190/90 Pulse 80 Weight 115 lbs Thyroid, $\frac{1}{2}$ gr daily

54 Letters received from patient and doctor Can do her housework No complaints Weight 109 lbs Pulse 78 BP 180/130

69 Report from doctor saying patient is fine No treatment for 6 to 8 months Very active Flatulence only complaint Weight 110 lbs Hgb 80% Pulse 72 BP 160/110 Thyroid, $\frac{1}{2}$ gr daily

Comment This case illustrates the importance of skull roentgenograms in what may appear to be spontaneous myxedema Blood pressure which is usually normal or low in hypopituitarism was elevated in this case Patient responded very well to treatment, and at present she feels fine by taking only small doses of thyroid The sequence of events is difficult to determine The following conjectures are possible primary myxedema, aneurysm pituitary deficiency, adrenal cortical insufficiency, lowering of blood pressure decrease of pressure in aneurysm increase in adrenocortical function and several other sequences are possible

PITUITARY ADRENAL INSUFFICIENCY

Family history Tuberculosis cancer and cardiovascular disease

Past medical Five pregnancies and 1 miscarriage

Chief complaint Vomiting weakness and fainting spells at stool for 1 year

History of present illness

BEFORE ADMISSION

2 years Mild vague headaches otherwise well

1 year Pyelitis with dysuria and lower abdominal pains scotoma and slight mental confusion Weakness with defecation and nausea at the

PROTOCOL XIII FIG 60

sight of food Recovered entirely in a few weeks

1 month Marked weakness, faintness vomiting spells shortly after eating and occasional hematemesis Constipation flatulence and vague epigastric pains unrelieved by food or vomiting Admitted to the hospital for study

Physical examination Age 70 female married Apathetic, dehydrated and evident weight loss but not cachectic Talks slowly at times is disoriented and aphasic Skin very dry, loose, pale and somewhat lemon

tinged Tongue normal Apical systolic murmur Pulse 64 BP 90/70 Uterus atrophic Arm and knee jerks absent Fundi—Grade 2 sclerosis

Laboratory data RBC 3,180,000 Hgb 65 in 73% WBC 5,200 to 9,200 Reticulocyte count 0.7 to 1% Blood sugar 64 to 148 mg % NPN 24 mg % Plasma cholesterol 156 mg % Carbon dioxide combining power 49 volumes % BMR minus 24%

Progress Profound prostration, marked hypotension and hypoglycemic attacks during her hospitalization Attacks consisted of complete loss of consciousness, followed by partial recovery and then profound sleep with stertorous breathing At times she seemed mentally dull and stuporous Vomited at irregular intervals A mild urinary infection developed A diagnosis of adrenal insufficiency, secondary anemia and pyelonephritis was made Weight 110½ lbs Patient gradually improved with therapy

Treatment Intravenous fluids 10% glucose and saline Adrenalin ½ cc every 3 hrs, as necessary Eschatin 30 cc given for 17 days Sodium chloride 6 Gm (capsules) daily Liver extract (Lilly's concentrated) 7½ cc (intramuscular) Pyridium 1 tablet tid

Second hospital admission One year later Well except for occasional attacks of weakness and vomiting Recurrence of pyelitis and joint pains Admitted in profound shock markedly lethargic and responded very slowly to any questioning BP 68/50 Diagnosis—adrenal crisis With similar therapy given previously she improved daily BP reached 138/78

Next four years At times seemed quite well Appetite was good BP varied anywhere from 128 to 195 systolic However frequent similar spells of weakness collapse and unconsciousness occurred Nausea vomiting and marked anorexia were recurrent Pyelitis and joint pains too Treated at home with salt and eschatin in insufficient dosage

Third hospital admission About 4 years after first admission Admitted to the hospital in acute adrenal insufficiency Frequent bouts of nausea and vomiting Often mentally confused Gingivitis and pyelitis developed Improved slowly with previous

hospital regime Patient looked weak and lethargic Fundi—temporal pallor Skin smooth, scaly and shallow Axillary and pubic hair scant and fine Heart sounds faint BP 150/70 on admission Abdomen distended Knee joints tender, no swelling BMR minus 17 and 20% Poertgenographic film of skull—marked ballooning of the sella with practically complete destruction of posterior clinoids The depth of the sella is approximately 3 cm, left anterior clinoids show some erosion into the tuberculum Pineal gland shows no displacement by measurement Diagnosis—pituitary chromophobe adenoma

Fourth hospital admission Two months after third admission At intervals patient seemed well, however attacks of weakness, accompanied with nausea and vomiting mental confusion pallor, and loss of pulse would recur Painful knees often Patient was maintained on variable doses of adrenal cortical extract and responded fairly well On admission complained of weakness dry mouth, precordial pain and dyspnea Symptoms were such that they indicated a possible coronary occlusion BP 160/70 and 102/78 Urine normal RBC 3,760,000 Hgb 65% WBC 4,550 Blood sugar 128 mg % NPN 21 mg % Total protein 7.7 Gm % Blood chloride 553 mg % Serum sodium 122.3 to 147.4 mEq/l Serum potassium 8.8 to 17.8 mg % (day before death) EKG normal rhythm, low voltage QRS slurred all T waves low or flat Patient suddenly became worse and died Diagnosis—pituitary adenoma, with adrenal insufficiency and secondary pituitary cachexia

Postmortem findings Anatomic diagnoses Pituitary adenoma Adrenal cortical atrophy Bilateral hydrothorax Mihiary tuberculosis of lungs (healed) Ascites Moderate generalized arteriosclerosis Leiomyoma of uterus Chronic thyroiditis Microscopic diagnoses confirmed the gross anatomic findings Chromophobe adenoma of pituitary Atrophy of adrenals Chronic thyroiditis Mihiary tuberculosis of the lungs (healed)

Comment Initially adrenal insufficiency was recognized but the possibility of pituitary

tumor was not considered until later. This patient illustrates the importance of roentgenographic films of the skull in all cases of adrenal insufficiency and hypoglycemic shock, particularly where the usual and characteristic pigmentation of Addison's

disease is not present. She did very well in spite of unavailability of desoxycorticosterone, recurrent episodes of shock and adrenal insufficiency showing that a patient may live comfortably over a period of years with adequate therapy.

REFERENCES

- 1 De La Balze F A, Reifenstein E C and Albright F. Differential blood counts in certain adrenal cortical disorders (Cushing's syndrome, Addison's disease and panhypopituitarism). *J Clin Endocrinol*, 6: 312-319 (Apr) 1946.
- 2 Hurxthal L M. Unpublished data.
- 3 McCullagh E P, Lewis L A and Owen W F. Adrenal failure of pituitary origin: plasma protein studies (Tiselius) report of 4 cases. *Cleveland Clin Quarterly* 10: 88-104 (July) 1943.
- 4 Thorn H. *The Diagnosis and Treatment of Adrenal Insufficiency*, p. 53. Springfield Ill: Thomas, 1949.



FIG. 60. PITUITARY ADRENAL INSUFFICIENCY (See Protocol 7 XIII.) Adrenal insufficiency with recurrent hypoglycemia due to a chromophobe pituitary adenoma. Patient died at 75 years of age from what seemed to be an acute coronary infarction but this was not verified at autopsy. Generalized arteriosclerosis. No characteristic pigmentation of Addison's disease. Note normal and healthy appearance of patient.

SECTION ■

DIABETES INSIPIDUS

I DEFINITION	A disease characterized by polyuria, with a urine of very low specific gravity and polydipsia without glycosuria, the disorder may be persistent or characterized by relapses and remissions
II APPEARANCE	Normal or thin, unless complications or associated diseases
III AGE	Average 21 ⁶³ usually occurs before 10, rarely after 50 (incidence 16.5 per 100,000 capita ^{40 87})
IV SEX	Ratio, male to female 2:1
V MENTAL DEVIATIONS	Normal, occasionally intelligence lower than average
VI PHYSICAL STATUS	
A NUTRITION	Variable
B HEIGHT	Normal or decreased
C EXTREMITIES	Normal, feet may be edematous late in disease
D SPINE	Normal
E INTEGUMENT	Generally dry temperature may be subnormal
F HEAD	Throat may be dry fundi are normal, unless associated with an intracranial lesion
G NECK	Thyroid normal or colloid goiter may be found
H CHEST	Normal
I HEART AND PERIPHERAL VESSELS	Normal variations
J BREASTS	Normal
K ABDOMEN	Normal
L GENITALIA	Normal
M NEUROMUSCULAR	Normal tremor may be present or absent and reflexes variable depending on etiology
N SPEECH	Normal
VII LABORATORY DATA	
A URINE	
1 General	Large quantities, 5 to 20 liters or more/24 hrs, specific gravity very low—1.001 to 1.005
2 Special analyses	
a Sugar	Absent
b Albumin	Absent later may show slight amount
c Nitrogen	Normal ⁶⁵
d Creatinine	Normal ²²
e Creatinine	Normal
f Sodium	Normal
g Potassium	Normal
h Calcium	Normal ²²
i Phosphorus	Normal

j Chlorides	Normal or increased ^{18 22 77 40 60 77 78 83 83 110 111 117}
k Iodine	Normal or increased ¹²
l Magnesium	Normal ²²
m Uric acid	Normal
II HEMATOLOGY	
1 Red blood cells	Normal or increased occasionally decreased
2 Hemoglobin	Normal or increased occasionally decreased
3 White blood cells	Normal
4 Differential	Normal
5 Hematocrit	Normal (blood may show slight dilution without treatment) ^{15 17 117}
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal ^{7 13 17 22 64 73 79 87 110 111 113 117}
2 Nonprotein nitrogen	Normal ^{17 19 79 87 117 120}
a Urea nitrogen	Normal ^{2 7 9 113 116 117 170}
3 I protein	Normal ^{117 19 25 83 104 110 111}
a Total	Normal
b Albumin	Normal
c Globulin	Normal
d A/G ratio	Normal
4 Uric acid	Normal ^{24 117 170}
5 Cholesterol	Normal ^{17 19 73}
6 Sodium	Normal usually may be increased or decreased ^{18 22 79 116}
7 Potassium	Normal ^{25 73}
8 Calcium	Normal rarely increased ^{17 97 104 116 170}
9 Phosphorus	Normal ^{7 17 97 108 116}
10 Chlorides	Normal usually may be increased or decreased ^{2 16 11 1 22 70 73 80 104 110 111 120}
11 Iodine	Low normal (relation of inorganic to organic is normal) ¹⁷
12 Phosphatase	Normal
13 Creatinine	Normal ^{2 117}
14 Creatine	Normal
15 Total lipids	Normal ⁷³
16 Carbon dioxide combining power	Normal ¹¹⁷
D FUNCTION TESTS	
1 Tolerance	
a Glucose	Normal or occasionally diabetic curve ^{2 7 11 11 74 45 11 60 73 108 116 170}
b Glucose insulin	No data
c Insulin	No data
d Iodine	Normal or low ¹
2 Adrenal water	Normal ⁸³
3 Salt deprivation	Normal ¹³
4 Balance	
a Nitrogen	Normal ^{20 117}
b Calcium	No data
5 Renal	
a Phenolsulfonphthalein	Normal ^{7 13 79 116 120}
b Clearance	
(1) Urea	Normal ^{7 21 61}
(2) Creatinine	Normal ²⁰
(3) Inulin	Normal or decreased ^{80 2 1}

E MISCELLANEOUS TESTS

- | | |
|--------------------------------------|--|
| 1 Basal metabolic rate | Normal or decreased ^{17 19 73 10 1-1} |
| 2 Circulation time | Normal ¹⁸ |
| 3 Sedimentation rate | Normal |
| 4 Specific dynamic action of protein | No data, normal probably |
| 5 Gastric analysis | Normal, or higher degree of acidity greater volume of gastric juice, increased pepsin and renin ^{14 19} |
| 6 Electrocardiogram | Normal ⁷³ |
| 7 Blood volume | Normal ^{18 117} |
| 8 pH | No data |
| 9 Spinal fluid | Normal dynamics and content ^{18 19 9 110 10} |
| 10 Electroencephalogram | Normal or abnormal |
| 11 Venous pressure | Normal ¹⁸ |

F URINARY HORMONE ASSAYS

- | | |
|-----------------|---------------------|
| 17 ketosteroids | Normal ⁴ |
|-----------------|---------------------|

G BIOPSY

- | | |
|---------------|--------|
| 1 Endometrial | Normal |
| 2 Testicular | Normal |

H VAGINAL SMEAR

Normal probably

I SEMEN ANALYSIS

Normal probably

VIII ROENTGENOGRAPHIC FINDINGS**A SKULL**

- | | |
|-----------------|---------------------|
| 1 Cranial vault | Normal unless tumor |
| 2 Sella turcica | Normal size |
| 3 Sinuses | Normal |
| 4 Mandible | Normal |
| 5 Teeth | Normal |

B EPIPHYSEAL STATUS (bone age) Normal or retarded⁶**C LONG BONES** Normal**D VERTEBRAE** Normal**E BONE TEXTURE** Normal**F MISCELLANEOUS**

- | | |
|-------------------|--------|
| Gastro intestinal | Normal |
|-------------------|--------|

IX ETIOLOGY^{11 36 88 115}**A BASIC FACTOR**—Any lesion which produces a decreased formation and/or obstruction of posterior lobe secretions (see 88 VIII E)**B IDIOPATHIC (PRIMARY)^{15 17 19 93 12}****C SYMPTOMATIC (SECONDARY)**

- | |
|---|
| 1 Tumors—(other lesions, i.e., cysts, primary or secondary carcinoma) ^{3 79 15 19 31 43 49 67 90 98 109 1-1} |
| ■ Pituitary gland |
| b Hypothalamus ⁹⁸ |
| c Midbrain |

d Third ventricle

e Pinealoma^{61 70 100}

2 Postinfectious^{9 17 18 110 42 64 7 73 76 84 119 10}

a Chronic encephalitis (epidemic post vaccinal, etc.)

b Syphilis^{5 19 22 34 91 114 117 10}

c Tuberculosis^{58 114}

d Scarlet fever

e Measles⁵⁴

f Influenza

g Metastatic abscesses^{116 123}

h Rheumatic fever

3 Cerebral vascular

- 4 Traumatic³ 11 41 47 91 122
- 5 Postoperative—craniotomy
- 6 Hand Schuller Christian's disease^{60 91}
- 7 Laurence Moon Biedl syndrome

II FAMILIAL TENDENCY^{11 41 60 73}

X PATHOLOGY

A Gross

- 1 Idiopathic group
 - a Kidneys
 - (1) Enlarged
 - (2) Congested
 - b Ureters—dilated
 - c Bladder—hypertrophy
 - d Heart—normal
- 2 Secondary group
 - Findings as above
 - b Dependent on basic etiology

B Microscopic²⁸

- 1 Pituitary
 - a Pars anterior
 - (1) Normal
 - (2) Hyperplasia
 - (3) Cellular destruction
 - b Pars intermedia
 - (1) Normal
 - (2) Hyperplasia
 - c Pars nervosa
 - (1) Normal
 - (2) Colloid—increased
 - (3) Hyaline—increased
- 2 Thyroid
 - a Normal
 - b Hyperplasia with hyperthyroidism (see Protocol 8 \IV)

XI PATHOLOGIC PHYSIOLOGY

A TYPES OF DIABETES INSIPIDUS

- 1 Persistent—all symptoms remain permanently
- 2 Intermittent⁶⁹
 - a Symptoms may appear and disappear at irregular intervals
 - b During active stage serum contains substance that will inhibit antidiuretic action of posterior lobe extract
 - c During remission serum contains an excess of antidiuretic factor similar to effect of pitressin

B FACTORS INVOLVED

- 1 Deficient secretion of antidiuretic hormone is due essentially to hypofunction of posterior pituitary^{4 76 44}

- 2 If the anterior pituitary lobe's diuretic hormone cannot counterbalance the antidiuretic hormone of the posterior lobe then diabetes insipidus may develop

3 Occurrence of the disease only if

- a Functions of pars neuralis are severely damaged—at least over half must be nonfunctioning^{69 114}
- b Pars glandularis is active^{38 87 114}
- c There is injury of^{39 67 68}
 - (1) Suprapituitary hypophyseal tract
 - (2) Nerve centers at hypothalamic region
- d Adjacent lesions cause pressure on above areas
- e Patient has no serious disorder of
 - (1) Heart
 - (2) Kidneys
- f Thyroid gland is intact³⁴
 - (1) It is questionable that TSH is the diuretic principle of anterior pituitary
 - (2) Diuretic action of anterior pituitary is not mediated through thyroid alone

C PHYSIOLOGIC EFFECTS¹

- 1 Disturbance of exchange of salt and water in the
 - a Tissues
 - b Blood
- 2 Inability of the kidney tubules to reabsorb water in normal quantity^{1 38 64}
 - a Hormonal effect essentially and not nervous mechanism
 - b Plasma sodium chloride may be increased because of this
- 3 Specific gravity of blood increases, if dehydration is present⁷⁵

XII SYMPTOMATOLOGY

A Onset

- 1 Sudden after
 - a Injury
 - b Shock
 - c Infectious disease
- 2 Gradual—more common

B GENERAL

- 1 Polydipsia
- 2 Anorexia
- 3 Weight loss
- 4 Constipation
- 5 Polyuria

- 6 Impotence
- 7 Weakness
- 8 Headache
- 9 Vision
 - a Blurred sometimes
 - b Transient hemianopsia is common (syphilitic cases)
- C MARKED RESTRICTION OF FLUID INTAKE PRODUCES
 - 1 Cramps in
 - a Abdomen
 - b Legs
 - 2 Nausea
 - 3 Vomiting
 - 4 Diarrhea
 - 5 Weight loss
 - 6 Tachycardia
 - 7 Headache (may be intense)
 - 8 Faintness
 - 9 Exhaustion
 - 10 Sweating
 - 11 Hypothermia
 - 12 Psychic disturbances
 - 13 Collapse

XIII DIAGNOSIS

- A URINARY FINDINGS
 - 1 Daily output enormous, ranging from 5 to 50 liters
 - 2 Specific gravity is usually less than 1.010
 - a In a 24 hr urine specimen
 - b After refraining from fluids as long as possible (see 2 VIII E 1 c)^o
 - 3 Glycosuria is absent
 - 4 Salt loading test (see 2 VIII E 1 a)⁴
 - a Urinary output is increased
 - b Inability to concentrate salt in urine
 - 5 Salt restriction—see 2 VIII E 1 b^{7 13}
- B THIRST EXCESSIVE

XIV DIFFERENTIAL DIAGNOSIS

- A DIABETES MELLITUS
 - 1 Association with diabetes insipidus is rare^{7 9 50 80 10* 103 120}
 - 2 Urine
 - a Specific gravity—high
 - b Sugar present
 - 3 Sugar (blood)—elevated
 - 4 Glucose tolerance—decreased
- B HYPERPARATHYROIDISM (see 38 VIII)
 - 1 Calcinuria in excess

- 2 Phosphorus (serum)—decreased
- 3 Calcium (serum)—increased
- C FUNCTIONAL POLYURIA
 - 1 Habit of drinking excessive amounts of fluids
 - 2 Enormous intake of fluids can be restricted without discomfort, specific gravity of urine will be over 1.010
 - 3 Kidneys can concentrate chlorides
 - 4 Symptoms are transient
 - 5 Evidence of a psychiatric condition may be noted
 - 6 Pitressin effects, if any, are limited
 - 7 Adrenal water test—negative
- D CHRONIC NEPHRITIS
 - 1 Urine contains
 - a Albumin
 - b Casts
 - 2 Renal function decreased
 - 3 Associated cardiovascular disease may be found

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A DIABETES MELLITUS—Both diseases may occur together, but rarely^{7 9 50 80 10*, 103 149}
- B HAND SCHULLER CHRISTIAN'S SYNDROME—see 92 V E 4
- C LAURENCE MOON BIEDL SYNDROME—see 95
- D HYPERTHYROIDISM—see Protocol 8 XIV 71 73

XVI TREATMENT

- A GENERAL MANAGEMENT
 - 1 Diet
 - a Low salt intake may be helpful to decrease urinary
 - (1) Volume
 - (2) Chloride concentration
 - b Protein foods in large amounts have been suggested
 - 2 No attempt should be made to reduce fluid intake
 - 3 Syphilitic treatment if indicated
 - 4 Lumbar puncture—cures have been reported following this procedure possibly due to lowered pressure of cerebrospinal fluid—^{46 59 107}
 - 5 Thyroid ablation^{1 17 21 34 71 111 11*}
 - a Reduction sometimes in
 - (1) Polyuria
 - (2) Iodine excretion

- 4 Traumatic^{9 28 31 37 38 100}
- 5 Postoperative—craniotomy
- 6 Hand Schuller Christian's disease^{100 91}
- 7 Laurence Moon Biedl syndrome

D FAMILIAL TENDENCY^{11 14 29 3}

X PATHOLOGY

A GROSS

- 1 Idiopathic group
 - a Kidneys
 - (1) Enlarged
 - (2) Congested
 - b Ureters—dilated
 - Bladder—hypertrophy
 - d Heart—normal
- 2 Secondary group
 - a Findings as above
 - b Dependent on basic etiology

II MICROSCOPIC³⁶

- 1 Pituitary
 - a Pars anterior
 - (1) Normal
 - (2) Hyperplasia
 - (3) Cellular destruction
 - b Pars intermedia
 - (1) Normal
 - (2) Hyperplasia
 - c Pars nervosa
 - (1) Normal
 - (2) Colloid—increased
 - (3) Hyaline—increased
- 2 Thyroid
 - a Normal
 - b Hyperplasia with hyperthyroidism
(see Protocol 8 \IV)

XI PATHOLOGIC PHYSIOLOGY

A TYPES OF DIABETES INSIPIDUS

- 1 Persistent—all symptoms remain permanently
- 2 Intermittent⁶⁹
 - a Symptoms may appear and disappear at irregular intervals
 - b During active stage serum contains substance that will inhibit antidiuretic action of posterior lobe extract
 - c During remission serum contains an excess of antidiuretic factor, similar to effect of pitressin

II FACTORS INVOLVED

- 1 Deficient secretion of antidiuretic hormone is due essentially to hypofunction of posterior pituitary^{6 26 44}

- 2 If the anterior pituitary lobe's diuretic hormone cannot counterbalance the antidiuretic hormone of the posterior lobe then diabetes insipidus may develop

- 3 Occurrence of the disease only if
 - a Functions of pars neuralis are severely damaged—at least over half must be nonfunctioning^{68 114}
 - b Pars glandularis is active^{39 8 114}
 - c There is injury of^{37 89}
 - (1) Supraoptico hypophyseal tract
 - (2) Nerve centers at hypothalamic region
 - d Adjacent lesions cause pressure on above areas
 - e Patient has no serious disorder of
 - (1) Heart
 - (2) Kidneys
 - f Thyroid gland is intact³⁴
 - (1) It is questionable that TSH is the diuretic principle of anterior pituitary
 - (2) Diuretic action of anterior pituitary is not mediated through thyroid alone

C PHYSIOLOGIC EFFECTS¹

- 1 Disturbance of exchange of salt and water in the
 - a Tissues
 - b Blood
- 2 Inability of the kidney tubules to reabsorb water in normal quantity^{1 88 94}
 - a Hormonal effect essentially and not nervous mechanism
 - b Plasma sodium chloride may be increased because of this
- 3 Specific gravity of blood increases if dehydration is present³⁵

XII SYMPTOMATOLOGY

A ONSET

- 1 Sudden after
 - a Injury
 - Shock
 - c Infectious disease
- 2 Gradual—more common

B GENERAL

- 1 Polydipsia
- 2 Anorexia
- 3 Weight loss
- 4 Constipation
- 5 Polyuria

DIABETES INSIPIDUS AND PRIMARY HYPERTHYROIDISM

Protocol XIV

Family history Cardiovascular disease*Past medical* Pneumonia and hives*Chief complaints* Weight loss for 5 months and excessive thirst*History of present illness* Fractured skull 4 years ago, resulting in polydipsia and polyuria Voided almost every hour night and day Five months before admission noted tremor and decrease in weight, a total loss of 30 lbs*Physical examination* Age 40, male Weight 137½ lbs Height 66¼ in Pulse 126 BP 150/80 Very toxic Tremor Thyroid slightly enlarged and firm*Laboratory data* Specific gravity of urine after 9 hrs without fluids 1.002 Total output 7 quarts/24 hrs BMR plus 70%*Treatment and progress* Nasal insufflations with pituitary powder relieved the poly-

dipsia and polyuria Gradual reduction of BMR to minus 7% in 2 months with methylthiouracil Gained 18 lbs Subtotal thyroidectomy Condition 11 months later, BMR plus 10% Weight 144 lbs Pulse 68 No trouble with thirst, except when over heated

Comment There was no decrease in diabetic insipidus symptoms for 4 years after skull fracture Hyperthyroidism probably began with onset of weight loss The effectiveness of insufflation of pituitary powder which was given simultaneously with methylthiouracil does not permit evaluation of role played by the latter drug In any event a "cure" of both disorders was accomplished by methylthiouracil and a subtotal thyroidectomy

REFERENCES

- Allen A A and Stokes J S Cure of diabetes insipidus coincident with bilateral correction of abdominal cryptorchidism by gonadotrophic factor from pregnancy urine JAMA 106 780 781 (Mar) 1936
- Allen F M and Sherrill J W Diet treatment of diabetes insipidus J Metabolic Research 3 479 510 (Mar) 1923
- Arnstein A Diabetes insipidus bei metastatischer Karzinose der Hypophyse namentlich des Hinterlappens bei primarem Bronchus- und Mammakarzinom Med Klin 29 1679 1681 (Dec) 1933
- Artaud A Un cas de grossesse au cours d'un diabète insipide Bull Soc d'obst et de gynec 22 196 193 (Feb) 1933
- Babonneix L and Lhermitte J Diabetes insipidus from encephalitis of infundibulum and tuber cinereum of syphilitic origin Ann de med 18 471 478 (Dec) 1925
- Baker A H and Craft C B Bilateral localized lesions in hypothalamus with complete destruction of neurohypophysis in pituitary dwarf with severe permanent diabetes insipidus Endocrinology 26 801 806 (May) 1940
- Bernstein M Moore M T and Fishback D B Diabetes insipidus as a sign of metastatic involvement of the supra-optic hypothalamic system Arch Int Med 62 604 617 (Oct) 1938
- Biggart J H Diabetes insipidus site of formation of anti diuretic hormone Edinburgh MJ 43 417 425 (July) 1936
- Diabetes insipidus Bram 58 86 96 (Mar) 1935
- Bleakley J A case of diabetes insipidus and twin pregnancy Proc Roy Soc Med 31 1062 1064 (July) 1938
- Blotner H Inheritance of diabetes insipidus Am J M Sc 204 261 265 (Aug) 1942
- The amount of iodine in blood and urine in patients with diabetes insipidus Am J M Sc 203 708 717 (May) 1942
- Effect of amniotin and antuitrin S in diabetes insipidus New England J Med 217 592 594 (Oct) 1937
- Gastric analyses and gastric symptoms in diabetes insipidus Am J Digest Dis 7 73 75 (Feb) 1940
- Pitressin tannate in oil in treatment of diabetes insipidus JAMA 119 995 997 (July) 1942
- Blood and urine chlorides in 22 cases with diabetes insipidus Am J M Sc 202 222 229 (Aug) 1941
- Blotner H and Cutler C Total thyroidectomy in treatment of diabetes insipidus JAMA 116 2739 2745 (June) 1941
- Blotner H and Kunkel P Diabetes insipidus and pregnancy report of 2 cases New England J Med 227 287 292 (Aug) 1942
- Blumgart H L Diabetes insipidus with particular reference to further experience with treatment by pituitary posterior lobe extract applied intranasally M Clin North America 15 895 903 (Jan) 1932
- Brown W E Jr and Rynearson H H Procedure for diagnosis of diabetes insipidus Proc Staff Meet Mayo Clin 19 67 68 (Feb) 1944
- Butler A M Harper E A and Carey W W Jr Excretion of sodium and chloride in normal persons and in patients with nephritis and diabetes insipidus Am J Dis Child 46 1459 1460 (Dec) 1933
- Cambridge P J Complete recovery from diabetes insipidus Practitioner 105 244 247 (Oct) 1920
- Carter P J Diabetes insipidus in pregnancy case report Urol & Cutan Rev 44 549 551 (Sept) 1940

- b Subsequent myxedema is treated with desiccated thyroid
- c Value questionable as a universal procedure
- 6 Diuretics may relieve some symptoms
- 7 Surgical—see 13 VII¹⁰

II ROENTGEN¹⁰ 106 11

- 1 Indicated in the following
 - a Neoplasms of pituitary and surrounding areas
 - b Hand Schuller Christians disease
- 2 Results may be satisfactory

C HORMONAL

- 1 Pituitrin (specific)
 - a Preparations
 - (1) Powder used as snuff or by insufflation¹⁰
 - (a) Dosage—by trial and error average 2 to 3 times a day¹⁰
 - (b) Contraindication — allergy to powder¹⁰
 - (2) Suspension in oil—intramuscular¹⁰ 106 122
 - (a) One cc. containing 5 pressor units may relieve symptoms for 30 to 82 hrs
 - (b) 0.25 to 0.30 cc. can be used in daily doses but often followed by reactions (see below)¹⁰
 - (3) Pellets—unsatisfactory because of local and/or general reactions¹⁰
 - b Results
 - (1) Antidiuretic effect (kidney threshold for excretion of water raised)
 - (2) Specific gravity of urine increased
 - (3) Water balance becomes positive
 - (4) Urinary excretion of the following is decreased
 - (a) Nitrogen
 - (b) Chlorides (unchanged some times)
 - (5) Relative decrease of
 - (a) Total nitrogen
 - (b) Sodium chloride of plasma
 - (6) Slight increase in plasma volume
 - (7) Chlorides (serum) become normal
 - (8) Thirst less severe

- c Effects of overdosage
 - (1) Oliguria
 - (2) Water retention
 - (3) Weight gain may be rapid
 - (4) Headache
 - (5) Restlessness
 - (6) Drowsiness
 - (7) Fainting
 - (8) Weakness
 - (9) Pallor
 - (10) Menstrual flow may be increased in
 - (a) Amount
 - (b) Duration

D MISCELLANEOUS

- 1 Comment—the following medications are of variable and questionable value
- 2 List
 - a Antutrin 'S' ¹
 - b Intermediate lobe preparations¹⁰
 - c Thyroid (desiccated U.S.P.)
 - d Desoxycorticosterone¹⁰
 - e Testosterone (if an associated testicular deficiency is present)¹⁰
 - f Estrogens¹⁰ 106
 - g Amidopyrine¹⁰ 106 108

XVII PROGNOSIS

- A IDIOPATHIC
 - 1 Long life usually, 50 years average
 - 2 Spontaneous cessation or remissions in some
- B SYMPTOMATIC
 - 1 Outcome depends on pathologic lesion
 - 2 Fatality may come early
- C PREGNANT PATIENT¹ 10 13 23 25 29 54 55, 58 74 87 97 113
 - 1 Symptoms may
 - a Increase
 - b Improve
 - c Remain unaltered
 - d Develop in any stage
 - 2 Outcome as for others without complications

XVIII CAUSES OF DEATH

- A ALCOHOLISM
- B PNEUMONIA
- C PRIMARY LESION
- D COMA

- 65 Kahn H S Use of amidopyrine in case of diabetes insipidus JAMA 100 1593 1594 (May) 1933
- 66 Levit S G and Pessikova L N Genetics of diabetes insipidus and its bearing on problem of dominance in man J Hered 27 445-448 (Nov) 1936
- 67 Macchiore G Su un caso di diabete insipido da tumore metastatico della regione ipofisaria Minerva med 1 668 672 (May) 1935
- 68 Magoun H W and Ranson S W Role of supra opticohypophyseal tract and neurohypophysis in regulation of water exchange in monkey Tr Am Neurol A 65 63 66 1939
- 69 Mainzer F Über Fragen der Hypophysenhinterlappentherapie des Diabetes insipidus Wien Arch f inn Med 26 101 120 1935
- 70 Martin J and Davis J Syndrome of destruction of the pineal gland Experimental and clinical observations Arch Int Med 67 1119 1131 (June) 1941
- 71 McConnell A A A case of diabetes insipidus influenced by partial thyroidectomy Irish J M Sc pp 742 745 (Dec) 1936
- 72 McGavack T H Benjamin J W and Liebowitz S Diabetes insipidus Arch Neurol & Psychiat 44 867 878 (Oct) 1940
- 73 McGavack T H Boyd L J and Gelvin P Experimental modification of water and salt output in patients with diabetes insipidus J Clin Endocrinol 2 551 559 (Sept) 1942
- 74 McLaren H C and McLeod M Case of diabetes insipidus in pregnancy J Obst & Gynaec Brit Emp 49 51 58 (Feb) 1942
- 75 McPhedran H Three cases of diabetes insipidus one associated with toxic goitre Canad M A J 39 370 373 (Oct) 1938
- 76 Moore R A and Cushing E H Diabetes insipidus and Frohlich's syndrome associated with encephalitis of the hypothalamic region Arch Neurol & Psych 34 828 832 (Oct) 1935
- 77 Oppenheim H Casuistischer Beitrag zur Polyurie Ztschr f klin Med 5 618 620 1882
- 78 — Weiterer Beitrag zur Polyurie Ztschr f klin Med 6 556 559 1883
- 79 Peabody F W Report of a case of diabetes insipidus Tr A Am Physicians 40 170 176 1925
- 80 Rabinowitch I M Metabolic studies on a case of diabetes insipidus Arch Int Med 28 355 (Sept) 1921
- 81 Rand C W and Patterson G H Traumatic diabetes insipidus report of 6 cases Bull Los Angeles Neurol Soc 2 163 171 (Dec) 1937
- 82 Richter C P Experimental diabetes insipidus its relation to the anterior and posterior lobes of the hypophysis Am J Phys 110 439 447 (Dec) 1934
- 83 Robinson F J Power M H and Kepler E J Two new procedures to assist in the recognition and exclusion of Addison's disease a preliminary report Proc Staff Meet Mayo Clin 18 577 582 (Sept) 1941
- 84 Roehm H R Postvaccinal encephalitis associated with diabetes insipidus Am J Dis Child 44 1293 1296 (Dec) 1932
- 85 Rosenbloom J and Price H T A metabolic study of diabetes insipidus Am J Dis Child 12 53 60 (July) 1916
- 86 Rowntree L G Diabetes insipidus JAMA 83 399 405 (Aug) 1924
- 87 — Diabetes insipidus Oxford Medicine 4 179 192 1921
- 88 Rutherford R H and Griffith J Q Jr Pitressin inhibiting substance in serum of patient with transient diabetes insipidus J Clin Endocrinol 1 916 917 (Nov) 1941
- 89 Rutledge D I and Rynearson E H Diabetes insipidus coexistence of diabetes mellitus and diabetes insipidus Proc Staff Meet Mayo Clin 14 441 443 (July) 1939
- 90 Sekiguchi Shigeki Hypophyseal disorder in mammary cancer and its relation to diabetes insipidus Ann Surg 53 297 304 (Mar) 1916
- 91 Sequeira J H Syphilitic gummatous in a patient with diabetes insipidus Brit J Dermat 27 186 188 (May) 1915
- 92 Shapiro B Control of urinary secretions by the anterior pituitary Lancet 2 1457 1460 (Dec) 1938
- 93 Smith F M Diabetes insipidus treatment by intranasal insufflation of posterior lobe pituitary powder JAMA 102 660-664 (Mar) 1934
- 94 Smith H W The excretion of water Bull New York Acad Med 23 177 195 (Apr) 1947
- 95 Snell A M and Rowntree L G Clinical manifestations of water intoxication in case of severe diabetes insipidus with some notes on disturbances of blood composition and a motor mechanism Endocrinology 11 209 223 (May June) 1927
- 96 Sosman M C Xanthomatosis (Schuller's disease) report of 3 cases treated with roentgen rays Am J Roentgenol 23 581 597 (June) 1930
- 97 Soule S D Diabetes insipidus and pregnancy Am J Obst & Gynec 33 878 880 (May) 1937
- 98 Spain A W and Geoghegan F Diabetes insipidus in association with postpartum pituitary necrosis J Obst & Gynaec Brit Emp 53 223 227 (June) 1946
- 99 Staemmler M Diabetes insipidus und Hypophyse Ergebn d allg Path u path Anat 26 59 86 1932
- 100 Stephens D J Pitressin in oil Prolonged antidiuretic effect in experimental and clinical diabetes insipidus J Clin Investigation 20 463 (July) 1941
- 101 Stringer S W Diabetes insipidus associated with pinealoma implant in the tuber cinereum Yale J Biol Med 6 375 383 (Mar) 1934
- 102 Sulzberger M D Pituitary hormone intermediate as active antidiuretic in treatment of diabetes insipidus preliminary report JAMA 100 1978 1930 (June) 1933
- 103 Sweeney J S Coexistent diabetes mellitus and diabetes insipidus with case report Endocrinology 13 477 483 (Sept Oct) 1929
- 104 Talbot J H Coombs F S Consolazio W V and Pecora L J Diabetes insipidus associated with diabetes mellitus metabolic studies and report of case Arch Int Med 65 607 624 (Sept) 1940
- 105 Thorn G W and Stein K Pitressin in tamate therapy in diabetes insipidus J Clin Endocrinol 1 680 687 (Aug) 1941
- 106 Towne E C Cessation of diabetes insipidus on roentgenray treatment of pituitary gland JAMA 103 2085 2087 (Dec) 1924
- 107 Trouser J Action antipolyurique des hautes doses de folliculine dans le diabète insipide de

- 24 Carter A C and Robbins J The use of hypertonic saline infusions in the differential diagnosis of diabetes insipidus and psychogenic polydipsia *J Clin Endocrinol* 7 753 766 (Nov) 1917
- 25 Chu H I Liu S H and Yu T F Water and electrolyte metabolism in diabetes insipidus *Proc Soc Exper Biol & Med* 46 682 685 (Apr) 1941
- 26 Corey E L and Britton S W Course of diabetes insipidus following hypophysectomy in rat *Proc Soc Exper Biol & Med* 46 678 679 (Apr) 1941
- 27 Curtis M M Production of experimental diabetes insipidus *Arch Int Med* 34 801 876 (Dec) 1924
- 28 Duncan J M Case of pregnancy and miscarriage complicated by diabetes insipidus *Tr Edinburgh Obst Soc* 3 353 354 1873
- 29 Duvour M Pollet L and Carcin M Diabète insipide suivi de diabète sucré avec coma Influence des grossesses sur la polyurie Traitement par la folliculine *Bull et mém Soc méd d hôp de Paris* 48 1444 1450 (Nov) 1932
- 30 Eaves E C and Croll M M The pituitary and hypothalamic region in chronic epidemic encephalitis *Brain* 53 56 75 (Apr) 1930
- 31 Elmer A W Kedzierski J and Schepps M Ein Fall von Diabetes insipidus verursacht durch eine Metastase eines Hypernephroms im Zwischenhirn Beitrag zur Pathogenese des Diabetes insipidus *Wien klin Wchnscrh* 41 591 594 (Apr) 1928
- 32 Ferro Luzzi G La throidectomia totale nel diabete insipido *Minerva med* 2 557 559 (Nov) 1937
- 33 Findley T Jr Thyroid pituitary relationship in diabetes insipidus *Ann Int Med* 11 701 713 (Nov) 1937
- 34 Findley T Jr and Hembecker P Total thyroidectomy for human diabetes insipidus *Proc Soc Exper Biol & Med* 36 448 449 (May) 1937
- 35 Findley T Jr and White H L Response of normal individuals and patients with diabetes insipidus to ingestion of water *J Clin Investigation* 16 19 202 (Mar) 1937
- 36 Fink B Diabetes insipidus clinical review and analysis of necropsy reports *Arch Path* 6 102 120 (July) 1928
- 37 — Diabetes insipidus associated with syphilis of hypophysis *Endocrinology* 10 317 326 (May June) 1926
- 38 Fisher C Ingram W R and Panson S W Diabetes insipidus and the neurohormonal control of water balance a contribution to the structure and function of hypothalamo-hypophyseal system *Ann Arbor Michigan Edwards Bros* 1938
- 39 — Relation of hypothalamo-hypophyseal system to diabetes insipidus *Arch Neuro & Psychiatry* 34 124 163 (July) 1935
- 40 Fitz R A case of diabetes insipidus *Arch Int Med* 14 706 721 (Nov) 1914
- 41 French H and Ticehurst C H Relation of traumatic diabetes insipidus to pheochromocytoma *Tr Clin Soc London* 39 117 122 1906
- 42 Fulgham J H and Berkuch J G Postvaccinal encephalitis *JAMA* 92 1427 1428 (Apr) 1929
- 43 Fletcher T B Diabetes insipidus and lesions of the mid brain report of a case due to metastatic tumor of hypothalamus *Am J M Sc* 178 837 852 (Dec) 1929
- 44 Geding E M K. and Oldham F A The neurohypophysis *JAMA* 116 302 306 (Jan) 1941
- 45 Gibson R B Magers J J and Dulancy H Blood sugar curves in diabetes insipidus and in habitual and experimental excessive water drinking *Endocrinology* 11 341 347 (July Aug) 1927
- 46 Graham E A Spinal puncture in diabetes insipidus *JAMA* 69 1498 1500 (Nov) 1917
- 47 — Diabetes insipidus as a sequel to a gun shot wound of the head *Ann Surg* 66 529 532 (Nov) 1917
- 48 Grant F C Surgical experience with tumors of the pituitary gland *JAMA* 136 668 672 (Mar) 1943
- 49 Grassman W Diabetes insipidus bei tumor metastasen in der hypophyse *Frankfurt Ztschr f Path* 42 384 393 1931
- 50 Gray W A and Moffat W M Coexistence of diabetes mellitus and diabetes insipidus case report with autopsy *Endocrinology* 27 430 433 (Sept) 1940
- 51 Greene J A and January L E Diabetes insipidus treated by subcutaneous administration of suspension of pituitary tannate in oil *JAMA* 115 1183 1185 (Oct) 1940
- 52 — Efficacy of pellets of posterior hypophysis and of pituitrin in oil in diabetes insipidus *Proc Soc Exper Biol & Med* 44 217 218 (May) 1940
- 53 Hall W W Diabetes insipidus case report following epidemic encephalitis with enormous polyuria *Am J M Sc* 165 551 562 (Apr) 1922
- 54 Harding F E Pituitary antidiuretic hormone in diabetes insipidus 8 cases of diabetes insipidus—4 with pregnancy *West J Surg* 51 269 288 (July) 1943
- 55 Hart S D and Breitman H B Diabetes insipidus complicating pregnancy *Am J Obst & Gynec* 41 527 528 (Mar) 1941
- 56 Healy J W Diabetes insipidus as a manifestation of general miliary tuberculosis *Brit J Child Dis* 32 275 283 (Oct Dec) 1935
- 57 Hembecker P and White H L Hypothalamo-hypophyseal system and its relation to water balance in dog *Am J Physiol* 133 582 593 (July) 1941
- 58 Hennet P Glucose et diabète en pratique obstétricale *Rev fr de gynéc et d'obst* 31 111 128 (Feb) 1936
- 59 Herrick J M Report of a case of diabetes insipidus with marked reduction in the amount of the urine following lumbar puncture *Arch Int Med* 10 17 (July) 1912
- 60 Hickey R C and Hare K The renal excretion of chloride and water in diabetes insipidus *J Clin Investigation* 23 768 775 (Sept) 1944
- 61 Horrax G The role of pinealomas in the causation of diabetes insipidus *Ann Surg* 426 725 739 (Nov) 1947
- 62 Hurthall L M Unpublished data
- 63 Jones H M Diabetes insipidus clinical observations in 42 cases *Arch Int Med* 74 81 93 (Aug) 1944
- 64 Jordan W R and Graham W R Diabetes insipidus following encephalitis *Virginia M Monthly* 69 35 37 (Jan) 1942

SECTION 9

GIGANTISM

- I DEFINITION**
Gigantism is characterized by a prepuberal hyperfunction of the pituitary growth hormone cells, causing height and rate of growth beyond normal age limits (see Fig 61)
- II APPEARANCE**
Strikingly and abnormally tall with slouchy posture otherwise normal during active stage of the disorder
- III AGE**
Usually begins in childhood or infancy if great height is reached,⁴ or may develop during puberty, causing acromegalic gigantism (see below), may follow period of relative dwarfism³⁴
- IV SEX**
Majority in males²⁵⁻²⁷
- V MENTAL DEVIATIONS**
- A INTELLIGENCE**
Variable may be feeble minded²⁷
- B RESPONSIVENESS**
Normal or subnormal
- C OTHER ABNORMALITIES**
Moody, irascible may become psychotic
- VI PHYSICAL STATUS**
- A NUTRITION**
1 Weight
Proportionate to height
2 Fat distribution
As in prepuberal habitus, rarely obese in active stage of growth
- B HEIGHT**
Final height depends on age of onset, duration and degree of pituitary activity (excluding presence of back deformity) may reach 108 in or more³⁻³³ abnormal rate of growth may be punctuated by periods of retarded growth (see Charts 18 to 21)³⁰
- C EXTREMITIES**
1 Upper
a Hands
Proportionate but may become eunuchoid later
b Fingers
Large
Proportionate but may become eunuchoid rarely arachnodactyly⁴⁵
c Span
Normal or may become greater than height
2 Lower
As for upper bony deformity around joints often genu valgum
a Feet
Proportionate may swell
b Toes
Exostoses and deformities may develop bunions and hammer toes from small shoes rarely arachnodactyly⁴⁵
- D SPINE**
Round back early later marked kyphosis and scoliosis may occur from osteoporosis
- E INTEGUMENT**
1 General
Normal or fine and soft if no sexual development
a Texture
Often subnormal³
b Temperature
Normal or excess
c Moisture

- l'homme Bull. et mêm Soc. méd. d. hôp. de Paris 48 1451 1455 (Nov.) 1932
- 107 Tucker J Immediate recovery from early diabetes insipidus after lumbar puncture Report of a case Am J M Sc 163 668 675 (May) 1922
 - 108 Turner H H Diabetes insipidus treatment with intermedin and pituitrin preliminary report of 5 cases Endocrinology 19 275 283 (May-June) 1935
 - 109 Urechia C I Cancer métabolique de la région hypophyso-tubérienne avec diabète insipide Paris méd 2 129 130 (Aug.) 1936
 - 110 Veil W H Über die Bedeutung intermediärer Veränderungen im Chlorstoffwechsel beim normalen und beim Nierenkranken Biochem Ztschr 91 267 316 (July) 1918
 - 111 — Über intermediäre Vorgänge beim Diabetes insipidus und ihre Bedeutung für die Kenntnis vom Wesen dieses Leidens Biochem Ztschr 91 317 380 (June) 1918
 - 112 Vercelli G Cure of post typhoid diabetes insipidus by deep x ray of diencephalic region Rev d. neurol 1 910-933 (June) 1934
 - 113 Vickers D M Diabetes insipidus with acute retention in pregnancy Surg Gynec & Obst 38 223 225 (Feb.) 1944
 - 114 Von Hann F Über die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus Frankfurt Ztschr f Path 21 337 365 1918
 - 115 Warkany, J and Mitchell A G Diabetes insipidus in children critical review of etiology diagnosis and treatment with report of 4 cases Am J Dis Child 57 603 666 (Mar.) 1939
 - 116 Weinstein F A and Spingarn C L A case of diabetes insipidus of inflammatory origin treated with roentgen rays J Mt Sinai Hosp 7 90-96 (July-Aug.) 1940
 - 117 Weir J E Observations on the influence of pituitary extract on the metabolism in diabetes insipidus Arch Int Med 32 617 634 (Oct.) 1923
 - 118 White H L and Findley T, Jr Responses of normal subjects and of patients with diabetes insipidus to water and salt ingestion J Clin Investigation 18 377 383 (July) 1939
 - 119 Whithead R W., and Darley W A case of diabetes insipidus occurring as a sequel to epidemic encephalitis Endocrinology 15 286 296 (July-Aug.) 1931
 - 120 Williams F Diabetes insipidus case report New York State J Med 30 103 1027 (Sept.) 1930
 - 121 Winer N J Renal function in diabetes insipidus Arch Int Med 70 61 87 (July) 1942
 - 122 Wyllie W G Diabetes insipidus its clinical features and treatment Proc Roy Soc Med 36 581 584 (Sept.) 1943
 - 123 Yaskin J C Lewey F H and Schwartz G A Diabetes insipidus and other unusual complications of acute purulent sinusitis clinicopathologic study of case Arch Neurol & Psychiat 48 119 127 (July) 1942

L GENITALIA

1 Male

a Penis

Normal, hypoplastic or proportionately enlarged, depending on age of onset (see Protocols 9 \V and \VII)

b Testes

As above (1a)

c Prostate

As above (1a)

2 Female

a External

As above (1a)

b Internal

As above (1a)

M NEUROMUSCULAR

1 Muscles

During active hypersecretory stage, may be unusually powerful but often easily fatigued

2 Gait

Leisurely, may be hampered by poor foot mechanics

3 Body movements

Handicapped by bulk, rare exceptions

4 Tremor

None, may be found if active hyperthyroidism is present

5 Paresthesias

None or may be observed if there is local extension of tumor

6 Reflexes

Normal unless extrasellar extension of tumor²³

N SPEECH

Normal but not lively

VII LABORATORY DATA

A URINE

1 General

Normal

2 Special analyses

a Sugar

May be found

b Creatine

Increased probably

c Creatinine

Increased probably

d Iodine

No data increased if thyroid hyperactivity present

B HEMATOLOGY

1 Red blood cells

Normal or low^{7 14 1}

2 Hemoglobin

Variable

3 White blood cells

Normal⁷

4 Differential

Normal^{7 14}

C BLOOD CHEMICAL ANALYSES

1 Sugar

Normal during growth period later may increase

2 Nonprotein nitrogen

Normal or below average^{7 21}

3 Protein

Normal⁷

4 Uric acid

Normal

5 Cholesterol

Variable, below average with pituitary overactivity¹ when diabetes present may be increased^{14 1}

6 Sodium

Normal

7 Potassium

Normal

8 Calcium

Normal

9 Phosphorus

No data presumably marked increase (6 to 7 mg %) based on findings in active acromegaly or acromegalic gigantism^{7 29}

10 Phosphatase

No data but should be increased in active state

11 Chlorides

Normal probably or low¹⁴

12 Iodine

No data should be increased especially if overactive thyroid function

13 Creatine

No data could be increased as in acromegaly

14 Creatinine

Increased

d Eruptions	Not common
e Pigmentation	Cafe au lait type circumscribed, freckles
f Color	Normal or sallow when pituitary becomes hypofactive
2 Hair	
a Head	Normal or luxuriant and coarse
b Facial	Depends on state of sexual development, usually slight amount
c Axillary	Depends on state of adrenal and gonadal activity (see 96 IV E) may be absent
d Pubic	As axillary may have female escutcheon
■ Body	May be increased if onset late in puberty, ¹⁷ or falls out later when hypofunction ensues
F HEAD	
1 Shape and size	Proportionate or slight brachycephaly (exceptions see Protocol 9 XVI) occasionally small leontiasis ossea facial hypertrophy ⁶
2 Facial expression	Normal or rather serious
3 Eyes	
a General	Normal exophthalmos rarely present with or without hyperthyroidism ^{28 24 4}
b Fundi	Normal papilledema or pallor of nerve heads
■ Visual	
(1) Fields	May be reduced bilateral hemianopsia possible
(2) Acuity	Normal or decreased
4 Ears and nose	Normal impaired sense of smell or anosmia deafness in some cases lobule may be absent (see Protocol 9 XV)
5 Mouth and throat	
a General	Normal or enlarged tongue
b Teeth	Normal or big
c Larynx (voice)	Proportionate to sexual development may be low if partially acromegalic
G NECK	
1 General	Normal or thin * Adam's apple prominent
2 Thyroid	Normal or increased in size
H CHEST	Proportionate except late in disease may be funnel or pigeon type ¹⁷
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal
2 Rate and rhythm	Normal or slow regular
3 Blood pressure	Normal to hypertensive diastolic is variable lower if hyperthyroidism is present
4 Peripheral arteries and veins	Normal
5 Vasomotor	See integument E 1
J BREASTS	
1 Male	May show colostrum ²⁴ occasionally pendulous
2 Female	Poorly developed
K ABDOMEN	
1 Liver	May be increased proportionately to general size
2 Spleen	Findings as for liver
3 Hernia	May be present
4 Tumor	None found

C LONG BONES

Some osteoporosis with sexual infantilism or marked hyperthyroidism, exostoses and overgrowth of tuberosities (compare with eunuch), increase in length of arms and legs when eunuchoid, radii greater than humeri, tibiae greater than femurs, necrosis of metatarsals may occur⁴⁵

D VERTEBRAE

Normal or wedging and osteoporosis, increased density (eburnization)⁴⁵

E BONE TEXTURE

Coarse trabeculations¹

F MISCELLANEOUS

1 Pelvis

May be feminine type²

2 Hip joints

Rarely osteochondritis deformans^{13 45}

3 Scaphoids (tarsal)

Occasionally Kohler's disease (fragmentation and increased density)⁴⁵

IX ETIOLOGY

A UNKNOWN

B HEREDITY—Possible tendency (see 9 XIV

C and Protocol 9 \VIII)^{10 41}

X PATHOLOGY

A GROSS^{3 8 33}

1 General splanchnomegaly which is often either

a Proportionate

b Disproportionate

2 Brain

a Normal⁴⁰b Enormous⁸

3 Pituitary tumor (see 2 IX A)

a Size—large,²⁶ but sometimes microscopic

b Surrounding tissues may be involved

4 Thyroid

a Small

b Enlarged

c Colloid goiter

5 Adrenals

a Small

b Large

6 Testes

a Involved

b Hyperplastic

7 Pancreas

a Small

b Marked fibrosis

c Very large

8 Thymus

a Involved

b Fatty tissue shreds

9 Spleen

a Normal

b Enlarged

10 Bones (see 9 VIII) ^{8 10 34}

a Overdeveloped

b Well formed

c Very long

d Thick

e Heavy

f Muscular insertions prominent

g Ridges very rough

h Hyperostoses

i Exostoses (see Fig 69)

j Deformity of feet

k Genu valgum

l Arthritis

m Osteosarcoma

n Kyphosis

o Scoliosis

B MICROSCOPIC³³

1 Pituitary (duration and treatment may change histology) (see 2 IX B 12 b)

a Hyperplasia of acidophilic cells proportionate to degree of activity but picture is variable due to other factors too (see Protocol 9 \VI)¹¹

b Many multinucleated cells

c Chromophobe adenoma or mixed types have been noted

d Cystic degeneration may be found occasionally⁸

2 Testes

a Seminiferous tubules

(1) Normal^{12 19 30}(2) Mere ghosts of acini with absence of Sertoli cells⁸(3) Hyalinization³

(a) Variable amounts present

(b) Few tubules may be normal

D FUNCTION TESTS

1 Tolerance

a Glucose

Normal probably except when adulthood is reached (see Protocol 9 \V)^{7 18 1}

b Glucose insulin

No data

c Insulin

No data

d Iodine

No data increased if hyperactivity of thyroid is present

2 Adrenal water

Normal unless pituitary becomes inactive¹

3 Salt deprivation

No data normal possibly or abnormal in burnt out cases

4 Balance

a Nitrogen

No data positive in active stage

b Calcium

No data negative possibly as in acromegaly

F MISCELLANEOUS TESTS

1 Basal metabolic rate

Variable^{14 1}

2 Circulation time

No data presumably normal unless elevated basal metabolic rate

3 Sedimentation rate

Normal

4 Specific dynamic action of protein

Normal or increased¹

5 Electrocardiogram

Normal

F URINARY HORMONE ASSAYS (see Acromegaly, 10 VII F)

1 FSH

Variable (see Protocol 9 \V)¹

2 LH

Not present

3 Estrogens

No data

4 Pregnanediol

No data

5 17 ketosteroids

Very low corresponding to gonadal and adrenal activity (see Protocol 9 \V)²¹

6 11 oxysteroids

No data

7 Aschheim Zondek

Negative²¹

8 TSH

No data

G Biopsy

1 Endometrial

Should be hypoplastic but depends on sexual development

2 Testicular

See microscopic pathology

H VAGINAL SMEAR

Estrogen effect reported²⁰

I SEMEN ANALYSIS

Normal or decreased count

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL

1 Cranial vault

Proportionately thickened or greatly increased occasion- ally open sutures hyperostoses (see Protocol 9 \VI),⁶ exostoses (see Figs 66 67 and 70)¹

2 Sella turcica

Normal rarely^{8 20 45} enlarged in most cases may decrease with roentgen therapy (see 2 \IV for measurements and Protocol 9 \V)²¹

3 Mandible

Proportionate increase in size except late in disease

4 Sinuses

Enlarged particularly frontals may be narrow

5 Teeth

Normal or perhaps enlarged

II EPIPHYSEAL STATUS (bone age)

Retarded often by several years²¹ (may remain un- united for many years³⁰) epiphyseal necrosis possible⁴⁵

- 5 17 ketosteroids—low
- 6 Sella—not larger than normal, but may be in individuals who were castrated very early in life
- C UNUSUAL TALLNESS OR "ATAVISTIC" GIGANTISM (see Figs 71 and 72)⁹
 - 1 Normal, but extremely tall individual
 - 2 Family history of unusual height
 - 3 Development normal and proportionate
 - 4 Sexual findings—normal
 - 5 17 ketosteroids—normal
 - 6 Sella—not enlarged
 - 7 Bone
 - a Changes—absent
 - b Age—often advanced 1 to 2 years
- D MACROGENITOSOMIA PRAECOX
 - 1 Differentiation should be made in early childhood
 - 2 Precocious development of (see 92 V F)
 - a Skeletal growth but final height is less than normal
 - b Somatic features
 - Genitalia
 - 3 17 ketosteroids—vary according to degree of precocity
 - 4 Sella—normal
- E HYPERTHYROIDISM — Evaluation of findings during childhood, see 26 VI B

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A GENERAL
 - 1 Tumor changes
 - a Intracranial extension
 - b Spontaneous decompression followed by⁴
 - (1) Sudden recovery of sight
 - (2) Relief from somnolence
 - 2 Anemia
 - 3 Fatigability
 - 4 Impotence
 - 5 Sterility
 - 6 Social and economic difficulties
 - 7 Susceptibility to infection (see 99 II)
 - 8 Diabetes
- B BONES
 - 1 Orthopedic problems
 - 2 Arthritis (hypertrophic)²⁰
 - 3 Osteosarcoma
 - 4 Osteoma
 - 5 Osteitis deformans

- 5 Polyostotic fibrous dysplasia (see Protocol 9 XVI, Figs 67 and 74)

7 Hyperostoses⁶

C MISCELLANEOUS

- 1 Hyperthyroidism (rare)
- 2 Syringomyelia (unusual)

XVI TREATMENT (see Figs 61, 73, 76 and Chart 21)

1 OF PITUITARY TUMOR

1 Roentgen¹⁵

a Indications

- (1) Abnormal growth rate
- (2) Evidence of tumor extension
- (3) Visual
 - (a) Fields defective
 - (b) Acuity impaired
- (4) Headaches

b Procedure—see 13 I\

c Subsequent management

- (1) Second series advocated in 2 months if

- (a) Growth rate is not satisfactorily retarded

- (b) Phosphorus (serum, fasting) above 5 mg %, for comparison the normal values are

- [1] Before puberty, about 5 mg %

- [2] After pubescence level declines to 3.5 mg % (average)

- (2) Later irradiation is advisable if

- (a) Abnormal growth rate resumes

- (b) Secondary complications develop

d Results

- (1) Abnormal growth retarded
- (2) Other symptoms may be relieved
- (3) Visual damages may be repaired
- (4) Phosphorus (serum) declines
- (5) Sella may decrease in size

2 Surgical¹⁰

- a Indication—if roentgen therapy fails to control

- (1) Growth
- (2) Expansion of lesion

b Procedures—see 13 VII

c Results

- (1) Growth acceleration—inhibited
- (2) Intracranial pressure—relieved
- (3) Phosphorus (serum)—decreases

- b Interstitial cells
 - (1) Number increased, but abnormal structure¹²
 - (2) Absent⁸
 - (3) Fibrotic replacement³
- c Spermatogenesis—decreased^{3 8}

- 4 Fatigued easily⁸
- 5 Weakness
- 6 Irrascibility
- 7 Depression
- 8 Impotence
- 9 Amenorrhea
- 10 Difficulties due to skeletal abnormalities

XI PATHOLOGIC PHYSIOLOGY

A EARLY IN DISORDER

- 1 Essentially an overproduction of growth hormone occurring in a prepubescent individual
- 2 Other hormonal factors may be normal or deficient especially
 - a Gonadotropins
 - b Adrenocorticotropin (probably)
- 3 Excess of growth hormone antagonizes adrenocorticotropin
- 4 Epiphyseal closure is thereby delayed thus permitting continued growth at an increased rate for an abnormal length of time
- 5 The changes are otherwise similar to acromegaly (see 10 I.), except for carbohydrate metabolism (see 2 VI B 3 d)

B LATE IN DISORDER—Overactivity of growth promoting hormone may subside and marked hormonal deficiencies possibly result due to

- 1 Pressure from tumor
- 2 Treatment
- 3 Atrophic (exhaustion) changes

XII SYMPTOMATOLOGY

A FACTORS

- 1 Degree of hyperactivity of acidophilic cells
- 2 Intracranial pressure by expansion or extension of tumor
- 3 Duration of disorder
- 4 Complications
- 5 Associated diseases

II COMMON COMPLAINTS

- 1 Growth which has
 - a Increased markedly
 - b Continued beyond normal
- 2 Headache
 - a Location—variable
 - b Pain
 - (1) Mild
 - (2) Extreme
 - c Nausea and/or vomiting may occur
- 3 Visual disturbances

XIII DIAGNOSIS

A SUMMARY

- 1 Growth rate
 - a Is abnormally increased
 - b Continues well beyond usual age of cessation
- 2 Sella turcica is enlarged in the majority of cases

B IMPORTANT DATA FOR CLINICAL STUDY

- 1 History
- 2 Physical examination
- 3 Previous measurements of height by checking school records to reveal time of
 - a Onset
 - b Rate of growth
- 4 Complete blood counts
- 5 Serum phosphorus (fasting)
- 6 Basal metabolic rate
- 7 Roentgenograms
 - a Skull
 - (1) Sella turcica—measurement of exact size
 - (2) Other changes
 - b Hand wrist for bone age
- 8 The following for future comparison
 - a Photographs
 - b Casts (face hands)
 - c Volume of water displacement by the extremities

XIV DIFFERENTIAL DIAGNOSIS

A ACROMEGALIC GIGANTISM^{1 14 19 22 27 31 33 37 43} (see Fig. 64)

- 1 Onset during or after pubescence
- 2 Acromegalic features are prominent
- 3 Sella turcica
 - a Enlarged in majority
 - b Normal occasionally

B EUNUCHOID GIGANTISM (hypogonadal gigantism)

- 1 Height—rarely over 7 feet
- 2 Span—greater than height
- 3 Acromegalic features—absent
- 4 Sexual organs—underdeveloped

[2] Pituitary may increase in size

[3] Growth may be retarded more effectively⁷⁹

C GENERAL

1 Anemia treated with iron or liver has little or no effect in these patients

2 Lassitude and/or somnolence—benzene sulfate (or similar preparations) dosage, oral—10 to 30 mg daily

3 Orthopedic problems

a Proper foot support

b Shoe fitting is important

c Attention to

(1) Scoliosis

(2) Kyphosis

d Osteomas are removed if necessary

e Epiphyses

(1) Irradiation should be considered in an 'all out' attempt to arrest growth

(2) Surgical treatment by exeresis

(a) Although not reported as having been done fixation of epiphyses might prevent unusual height if growth cannot be retarded otherwise

(b) Lower end of femurs and humeri would be sites of choice

4 Observations in the future for

a General condition

b Growth rate

c Visual field changes

d Phosphorus (serum) level

e Sella size

(1) Decrease

(2) Increase

D HYPERTHYROIDISM

1 Iodine (Lugol's solution)

a Administration

(1) Alone (see 26 XVI B)

(2) In combination with roentgen treatment

(3) After thiouracil preparation for surgery (see 26 XVI E)

b Dosage—oral, 10 minims tid pc in chocolate milk

2 Thiouracil derivatives (see 26 XVI D E)

a Dosage—daily

(1) Thiouracil—0.4 to 0.6 Gm

(2) Propylthiouracil—0.3 to 0.4 Gm

b Procedure—when basal metabolic rate is normal

(1) Reduce dose to one fourth of the original

(2) Start Lugol's solution preoperatively if surgery is planned

3 Roentgen therapy may be given over thyroid and/or pituitary to test its effectiveness (see 13 IX, 26 XVI G)

4 Subtotal thyroidectomy may be necessary after trial of above procedures

XVII PROGNOSIS (See Figs 61 65, 77)

A BENIGN TUMOR

1 Life expectancy is better than with malignant tumor nevertheless outcome is uncertain in either case

2 Average span is 21.3 years⁹

3 Few live to 50 years⁹

B THERAPEUTIC OUTLOOK

1 Logical and may be possible to arrest growth early but not enough patients have been treated

2 Recurrence of tumor after surgery has been observed

3 Sella may decrease in size

4 Secondary deficiencies may develop and require continued management

XVIII CAUSES OF DEATH

A INTERCURRENT INFECTION⁸⁰

B INTRACRANIAL EXTENSION OF TUMOR⁸¹

GIGANTISM	PROTOCOL XV	FIGS 61 62, 65, 66 69 73 75 76	CHARTS 18, 21
Family history	Patient much taller than brothers and sisters.	Chief complaint	Rapid growth '6 inches in previous 6 months
Past medical	Weighted 7¾ lbs at birth	Physical examination	Age 15 male single
Taller than average	at 4 to 5 years Did fairly well in school, but could not learn quickly	Weight	190 lbs
		Height	78¾ in (slightly stooped)
		Span	78¾ in
		Pubic bone to floor	40 in
		BP	112/75
		Shoe size	16
		Hammer	

d Postoperative irradiation (one series) is advisable about 2 weeks after surgery

3 Estrogens—see below

II HORMONAL

1 Indication—to promote sexual development if not present, thereby hastening
a Epiphyseal closure
b Growth cessation

2 Age for institution of therapy

a If pituitary gigantism is recognized and treated in childhood with roentgen therapy, hormones should be prescribed when normal adult height is

(1) Attained

(2) Probable within 5 years regardless of age²²

b Medication should be continued until bone age of at least 16 to 17 years has been reached

3 Preparations and dosages

a Gonadotropins (for males or females)

(1) Dosage—combined therapy parenteral²³

(a) Pituitary gonadotropins—150 to 300 ru daily

(b) Chorionic gonadotropin—500 to 2,000 ru daily

(2) Comment

(a) Patient may become resistant to these

(b) More practical to use than testosterone or estrogens

b Testosterone (for males)²⁷

(1) Dosage

(a) Oral — methyltestosterone 50 to 100 mg daily

(b) Intramuscular — testosterone propionate, 100 mg or more weekly

(c) Pellets — testosterone 200 to 400 mg every 2 or 3 months as indicated by rate of absorption

(2) Comment

(a) Theoretically with the reduction of excess growth hormone by roentgen therapy testosterone should hasten epiphyseal closure

(b) Following intensive roentgen therapy or surgery tes-

tosterone may be needed for its anabolic effects

c Estrogens (males and females)^{21, 24}

(1) Dosage

(a) Oral

[1] Stilbestrol — 0.5 to 5 mg daily (gradually increase)

[2] Estrone (or conjugated estrogens) — 0.6 to 6 mg daily

(b) Parenteral administration unnecessary

(2) Comment (see 10 XVI)

(a) Males

[1] Phosphorus (serum)

[a] Decrease suggests an inhibitory effect on growth (as in animals)

[b] Action on epiphyseal closure in gigantism is not known

[2] Objections (theoretical) may be overcome by simultaneous use of testosterone

[a] Breast enlargement possible

[b] Pituitary tumor size may increase

(b) Females

[1] Epiphyseal closure may be hastened (theoretical)

[a] Not by direct action but through the pituitary causing a release of adrenocorticotrophic hormone and gonadotropins

[b] With compression of cells by the pituitary tumor which make and store these factors it is doubtful that this action could take place until roentgen therapy has succeeded in relieving the pressure of the tumor

pubic hair Swelling of breast bone and ribs over heart between nipple and manubrium, kyphoscoliosis present Penis 7 cm long Testes $2\frac{1}{2} \times 1\frac{1}{2}$ cm Right hip larger than left

Laboratory data Urine albumin 1 plus, sugar trace RBC 4,370 000 Hgb 10.9 Gm WBC 5,000 Differential polymorphonuclears 68%, lymphocytes 28%, monocytes 2%, eosinophils 2% Blood sugar 88 mg % Plasma cholesterol 152 mg % BMR plus 4% Two years postoperative (mail report) serum calcium 12.9 mg %, serum phosphorus 4.2 mg %, serum phosphatase 3.7 BU

Roentgenographic findings Skull—large cranial vault with overdevelopment of sinuses Large osteoma (osteoblastic overgrowth) arising from right parietal and occipital areas, extending over to involve the left occipital bone, right maxillary sinus and maxilla Another osteoma originates from the sphenoid to obliterate sphenoid sinus Sella, which is not enlarged, is pushed upward and carries the entire middle fossa with it, anterior clinoids are separated Moderate mandibular prognathism Bone age 17 years Pelvis—female type with some separation of pubis Valgus deformity of both hips A peculiar cystic bony overgrowth (polyostotic fibrous dysplasia) in volving crest of right ilium

Treatment Operative note (abstract) by Dr

Gilbert Horrax Because of failing vision, an operation was undertaken as the best chance for recovering vision On account of the skull thickness the frontal sinus was deliberately opened with the usual bone flap The chiasmal region could not be exposed because of great tension, therefore, a tip of the right frontal lobe was quickly excised for adequate exposure A large dumbbell shaped tumor was extending from the sella under the frontal lobe, the upper end was about the size of a lime The tumor was sucked out, after opening and later removing the capsule Patient's condition was good during the procedure, which took 5 hrs Six postoperative roentgen treatments, 300 r each

Pathologic report Pituitary adenoma, chiefly chromophobe Bone—fibrosis and numerous osteoblasts and osteoclasts The pattern is unlike Paget's disease and more consistent with polyostotic fibrous dysplasia

Comment Gigantism with pituitary adenoma which was unrecognized until visual changes took place Sexual development slightly retarded Unusual bony overgrowth of skull and ilium with cystic areas in latter, possibly polyostotic fibrous dysplasia or simple hyperostosis Operative result for restoration of vision was excellent Patient incapacitated by bony deformities In view of his height, tumor may have had eosinophilic elements initially

PITUITARY GIGANTISM WITH NORMAL SEXUAL DEVELOPMENT

Family history Negative

Chief complaint Weakness

History of present illness At age of 8 years growth rate increased suddenly Height 160 cm at $10\frac{1}{2}$ years First seen by Dr Cushing in 1931 and reported by him (Dyspituitarism twenty years later, Arch Int Med 51:487-553 April 1933) A normally proportioned adolescent youth of 15, 5 ft $4\frac{3}{4}$ in tall (192 cm) and a span 7 cm greater than his height Weight 202 lbs Open epiphyses Roentgenograms of skull showed large accessory sinuses and a suspiciously large sella which measured 14 \times 17 mm Possible bitemporal defects in visual fields BMR normal BP 110/70 Pituitary

PROTOCOL XVII FIG 64

irradiated on 2 occasions (1932), and during following 12 months there was only $\frac{3}{8}$ in growth in comparison with 3 in previously Patient grew until 19 years of age, then measuring 6 ft $11\frac{1}{2}$ in Entered Army in 1942 Two years later he noticed weakness of his legs, but otherwise he was in good health Normal sexual drive

Physical examination Age 31 male single Weight 295 lbs Height 84 in BP 130/90 No prognathism Facial, body, axillary and pubic hair normal Visual fields and acuity normal Thyroid normal Testes large Absent ankle jerks Slight hyposthesia Left knee jerk diminished

Laboratory data Urine negative Hgb 13

toes, corns Skin pale Many freckles over face Head hair—long coarse dense, face, axillary and pubic hair are absent Facies normal Visual fields, acuity and optic disks normal Audiogram normal Penis and testes small Prostate not felt

Laboratory data RBC 3,400,000 to 4,400 000 Hgb 70% to 79% Blood sugar 69 mg % NPV 20 to 31 mg % Plasma cholesterol 92 to 170 mg % Glucose tolerance test normal Adrenal water test normal BMR minus 19% to minus 22% Urinary hormone studies FSH negative 17 ketosteroids 3.06 mg /24 hrs

Roentgenographic findings Skull on admission diameter 20 cm no change during observations Sella turcica 23 x 19 mm (790 sq mm), 6 years later 19 x 13 mm (387 sq mm) Frontal and maxillary sinuses grew larger Phalanges (terminal) tufting Heart not enlarged

MONTHS	BONE AGE	CHRONOLOGIC AGE
On admission	13	15
30	13	18
33	13.9	18
47	15.3	19
53	15.9	20
57	17.3	21

Treatment and progress Irradiation of pituitary during first 4½ years Patient grew 9 in in 6 years (see chart) No secondary sex characteristics after 2½ years of roentgen therapy Treated with chorionic and gonadotropic hormones from 2½ to 3½

years Dosage pituitary gonadotropin (300 ru per cc) 0.5 cc 6 times weekly, total 30 000 ru, and concurrently chorionic hormone of pregnancy urine (1,000 ru per cc) 1.5 cc 6 times weekly, total 300 000 ru Results of hormone therapy during first 3 months there was an increase in size of penis and testes with growth of pubic hair Erections and nocturnal emissions occurred By the tenth month, in spite of continued therapy there was a regression of all these changes Facial lanugo slight voice lower, and growth not stimulated Testosterone pellets 150 to 300 mg every 2 to 3 months, given for 5 to 5½ years Testosterone in propylene glycol (oral) irregularly Secondary sex characteristics, return of pubic hair, frequent erections voice deeper, growth (longitudinal) arrested epiphyseal closure stimulated with testosterone No benefit with iron for secondary anemia Benzedrine 5 mg bid for lassitude Weight 230 lbs Final height 87½ in Span 87½ in

Comment A typical pituitary giant, illustrating marked skeletal overgrowth with retarded bone age and without genital development beginning in early childhood The result of treatment was a slowing down of growth rate and epiphyseal closure concomitant with pituitary irradiation and administration of gonadotropic hormones and testosterone The case illustrates the presence of hypersecretion of growth hormone without evidence of excessive function of other pituitary hormones

GIGANTISM

Family history Other members tall

Past medical Age 7 to 8—increased height 74 in (tallest boy since first grade) Age 10 to 11—became deaf could not speak (an acute affair) Age 13—swelling of left side of face Age 15—diagnosed overactive pituitary but had no treatment In high school—eye changes first noted excellent student In college—good student Age 22—visual impairment severe

Chief complaint Trouble with his eyes

History of present illness Voice changed Beard absent Sexual development at high

PROTOCOL XVI Figs 63, 67, 68, 74

school age Growth of 4 in in 2 years Hemianopsia

Physical examination Age 23, male, single Weight 278½ lbs Height 79¼ in BP 140/110 Gloves size 11 Fundi optic atrophy bilateral and bitemporal hemianopsia Visual acuity right 10/200 and left 20/100 Right eye pushed upward due to prominence of tight cheek Right sided facial paralysis Slight rubor in cheeks Teeth far apart Tongue normal Nasal twang Collar size 17 Thyroid 1½ times normal size Skin smooth warm, moist Female type of

- 15 Hare H F Personal communication
- 16 Horrax G The Pituitary Gland pp 665 682
Baltimore Williams & Wilkins Co 1938
- 17 Humberd C D Gigantism of infantilism type
and its disclosure of pathogenesis of pigeon
breast and funnel chest Med Rec 147 444
449 (May) 1938
- 18 — Gigantism report of case JAMA 108
544 546 (Feb) 1937
- 19 — Gigantism, report of case South M J
II 988 992 (Sept) 1938
- 20 Hurvthal L M Further observations on
gigantism Lahey Clin Bull 3 136 142 (July)
1943
- 21 — Treatment of gigantism observations on
pituitary giant for 6 years J Clin Endocrinol
3 12 19 (Jan) 1943
- 22 — Pituitary gigantism Lahey Clin Bull
3 101 106 (Apr) 1943
- 23 Hurvthal L M and Horrax G Acromegalic
gigantism without enlarged sella turcica and
caused by probable pituitary tumor Lahey
Clin Bull 3 162 166 (Oct) 1943
- 24 Hurvthal L M Horrax G Hare H F and
Poppen J L The treatment of acromegaly
J Clin Endocrinol 9 126 148 (Feb) 1949
- 25 Hurvthal L M Unpublished data
- 26 Hutchinson W M The pituitary gland as a
factor in acromegaly and gigantism N Y
Med J 67 341 344 (Mar) 1898 and 67 450
453 (Apr) 1898
- 27 — The pituitary gland as a factor in acro-
megaly and gigantism N Y Med J 72 89
100 and 133 145 (July) 1900
- 28 Irgang S Striae atrophicae of gigantism Urol
& Cutan Rev 47 477 481 (Aug) 1943
- 29 Kinsell L W Michaels G D Le C H and
Larsen W E Studies in growth I Inter-
relationship between pituitary growth factor
and growth promoting androgens in acro-
megaly and gigantism II Quantitative evalu-
ation of bone and soft tissue growth in acro-
megaly and gigantism J Clin Endocrinol
8 1013 1036 (Dec) 1948
- 30 Launois P E., and Roy P Études biologiques
sur les géants Paris Masson 1904 p 50
- 31 Ibid pp 159 314
- 32 Ibid pp 355 378
- 33 Ibid pp 39-405
- 34 Mandl A Windholz F., and Rutil R III
nische rontgenologische und anthropometrische
Studien über einen Fall von Riesenwuchs nach
Wachstumshemmung Ztschr f d Neurol
u Psychiat 137 649 708 1931
- 35 McFarland J Notes on Mutter American
giant Tr & Stud Coll Physicians Philadel-
phia 6 148 158 1938
- 36 Mitchell J I Gigantism associated with
chronic polyarticular arthritis case report
Memphis M J 4 29-31 (Feb) 1927
- 37 de Neuville Nains et geants Revues des revues
(Jan) 1893
- 38 Reifstein E C Jr Kinsell L W and
Albright F Observations on the use of the
serum phosphorus level as an index of pituitary
growth hormone activity the effect of estrogen
therapy in acromegaly J Clin Endocrinol
6 40 (June) 1946
- 39 Rebin on W Notes on a giant Brit M J
1 560 (Apr) 1921
- 40 Rubinstein H S The Pituitary Gland p 50.
Baltimore Williams & Wilkins Co 1938
- 41 Schereschewsky N A Gigantism Endocrino-
logy 10 17 28 (Jan Feb) 1926
- 42 Seale E A Pituitary tumor—gigantism South
African M J 9 295 298 (May) 1935
- 43 Sternberg M Beiträge zur Kenntnis der Akro-
megalie Ztschr f klin Med 27 86 140 189
- 44 Sutton L P Abnormal growth in girl report
of case, Arch Pediat 44 109 115 (Feb) 1927
- 45 Traub E Epiphyseal necrosis in pituitary gi-
gantism Arch Dis Childhood 14 203 216
(Sept) 1939

Gm Serum calcium 10.5 mg % Serum phosphorus 4.1 mg % Glucose tolerance normal BMR minus 9% 17 ketosteroids 20.5 mg/24 hrs

Roentgenographic findings Skull showed large sinuses and mastoids, sella 20 mm x 15 mm 280 sq mm Spine and chest negative

Comment Clearly a case of pituitary gigantism initially considered due to hyperplasia of eosinophilic cells and not a tumor Meas-

urement of the lateral contour of the sella from the published skull roentgenogram (actual size) revealed an area of approximately 218 sq mm, indicating we believe an eosinophilic adenoma. It is assumed that local pressure effects of an expanding tumor were not sufficient to impair function of gonadotropic or other pituitary hormones. The muscular weakness of his legs was probably a peripheral neuritis occurring as the result of an acute upper respiratory infection.

ATAVISTIC GIGANTISM

Family history Grandfather was unusually tall. Parents normal.

Past medical At birth 9 lbs 5 oz, and 21 in. Participated in athletics. Mentally normal.

Chief complaint Growing too fast all his life.

History of present illness Patient grew about 2 to 2½ in a year. Between the ages of 12 to 13 he grew 4 in. and since then has averaged from 2 to 3 in a year.

Physical examination Age 15, male single. Weight 156½ lbs. Height 76 in. Span 79¾ in. BP 116/70. Body well proportioned. Hair normal. Genitalia normal. Other findings normal.

Laboratory data Urine complete blood count and glucose tolerance test normal. BMR minus 14%. Urinary FSH weak positive.

PROTOCOL XVIII FIGS 71, 72 CHART 20

17 ketosteroids 20.1 mg/24 hrs

Roentgenographic findings Skull normal. Bone age at 15 was 16 to 17 years. Terminal phalanges showed tufting.

Treatment None necessary.

Progress Final height 78¾ in. without shoes.

Comment This case illustrates an unusually tall individual who was normal in all other respects. His tallness might be considered atavistic in view of the great height of his grandfather in contrast with the normal stature of his parents. The possibility of a relative eosinophilic hyperplasia or adenoma cannot be excluded in these cases but failure of acromegalic changes after epiphyseal closure in most instances makes it unlikely.

REFERENCES

1 Achard C and Loeper M. Gigantisme acromégale et diabète. *Nouv icon de la Salpêtr* 13:398-403 1900.
2 Basso P. Endocrine growth disturbance—acromegaly gigantism dwarfism. *M Clin North America* 5:85-101 (July) 1921.
3 —. Gigantism and leontiasis ossea with report of the case of the giant Wilkins. *J Nerv & Ment Dis* 30:513 and 595 (Sept) 1903.
4 Biedl A. Innere Sekretion ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie. pp 312-315. Berlin und Wien Urban und Schwarzenberg 1910.
5 Brissaud H and Meige H. Gigantisme et acromégale. *J de méd et chir prat* 66:49-76 1895.
6 Buhl Un géant avec hyperostoses des os de la face et du crâne. p 301. *Mitteilungen aus dem pathologischen Institute zu München* 1878.
7 Turner F P, Frantz C H and Vander Meer H. Reduction of growth rate in gigantism treated with testosterone propionate. *JAMA* 117:515-516 (Aug.) 1941.
8 Cushing H. Pituitary Body and Its Disorders. pp 162-170. Philadelphia Lippincott 1912.
9 Dana C L. On acromegaly and gigantism with unilateral facial hypertrophy. cases with autopsy. *J Nerv and Ment Dis* 20:725-738 (Nov.) 1893.
10 Deluca F A. Gigantismo. *Arch Am de Med* 8:19 (Jan) 1932.
11 Dott N M, Bailey P and Cushing H. Hypophyseal adenomata. *Brit J Surg* 13:314-366 (Oct) 1925.
12 Downs W G Jr. Studies in sex interstitial cells in gigantism. *Am J Path* 5:295-302 (May) 1929.
13 von Dringl W and Diethelm L. R. Gressive skeletveränderungen bei hypophysärem Hochwuchs. Zugleich ein Beitrag zur Differentialdiagnose der Pertheschen Krankheit. *Klin Wchenschr* 16:628-632 (May) 1937.
14 Gray H. The Minneapolis Giant. *Ann Int Med* 10:1669-1682 (May) 1937.



FIG 63 PITUITARY GIGANTISM (See Protocol 9 XVI Figs 67 69 74) Height $79\frac{1}{4}$ in Kyphosis decreases natural height Note marked distortion of face due to bony overgrowth (See roentgenograms of skull and pelvis) Subnormal development of genitalia with female escutcheon Sella turcica is not enlarged anterior clinoids are separated Dumbbell shaped pituitary tumor occupying sella and protruding up under right frontal lobe Bilateral hemianopsia Pathologic diagnosis pituitary adenoma chiefly chromophobes



FIG 64 PITUITARY GIANT WITH NORMAL GENITAL DEVELOPMENT (See Protocol 9 XVII)

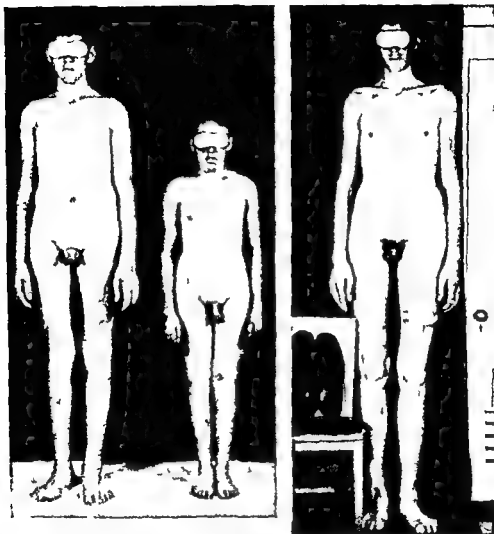


FIG 61 (Left) PITUITARY GIGANTISM (See Protocol 9 \V Figs 62 65 66 69 ,3 75 76 Charts 18 21) Patient age 15 beside boy of same age Before treatment Weight 190 lbs Height $78\frac{1}{4}$ in Span $78\frac{1}{2}$ in Pubis to floor 40 in

FIG 62 (Right) Six years later after roentgen chorionic and gonadotropic pituitary extract and testosterone therapy Weight 230 lbs Height $87\frac{1}{4}$ in Span $87\frac{1}{2}$ in



FIG 68 PITUITARY GIGANTISM (See Protocol 9 XVI Figs 63 67 74) Hand showing unusual position in which it was held by patient Glove size 11



FIG 69 PITUITARY GIGANTISM (See Protocol 9 XV Figs 61 62 65 66 13 75 76 Charts 18 21) Deformed toes as a result of wearing too small a shoe Obtaining proper shoes is one of the handicaps of being a giant Note also the coarse trabeculation and cystic changes in the terminal tarsal



FIG 70 ACROMEGALIC GIGANTISM (See Chart 19) Sella upper limits of normal (right 126 mm left 51 mm) Oxygen encephalogram shown above reveals tumor extending through posterior capsule also some dilatation of anterior horn and body of left ventricle Note also prominent sinuses and prognathism Hemiplegia present on left

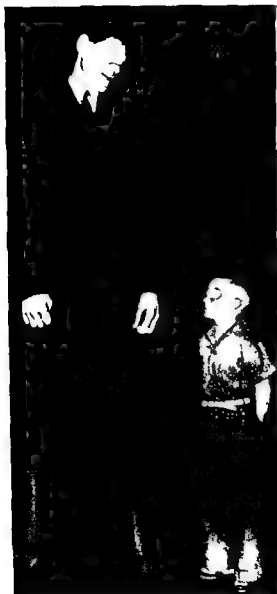


FIG 65 PITUITARY GIANT AND DWARF
Pituitary giant (Protocol 9 \V) beside pituitary dwarf (Protocol 3 IV) Prepubertal hypopituitarism of approximately same age 21



FIG 66 (Top) SKULL OF PITUITARY GIANT (See Protocol 9 \V Figs 61 62 63 69 73 75 76 Charts 18 21) Brachycephalic type Prominent sinuses enlarged sella no unusual prognathism

FIG 67 (Bottom) PITUITARY GIGANTISM (See Protocol 9 \VI Figs 63 64 74) Skull showing marked overgrowth of bone (polyostotic fibrous dysplasia) Bone in some parts 1 1/2 in thick Sella contour not visible Large frontal sinuses Little if any prognathism





FIG 71 UNUSUAL TALLNESS (See Protocol 9 \VIII Fig 72 Chart 20) Unusually tall boy of 15 Height 76 in Span 7934 in Bone age 16 to 17 Predicted final height from bone age was 78 in Actual final height 7834 in Although parents were not exceptionally tall (both under 72 in) the grandfather was regarded as a giant



FIG 72 SKULL OF UNUSUALLY TALL BOY (See Protocol 9 \VIII Fig 71 Chart 20) Except for normal size sella (52 sq mm) and normally shaped skull there is little difference between this skull and that of the pituitary giant pictured in Figure 66



FIG 73 PITUITARY CIGANTISM (See Protocol 9 XV Figs 61 62 65 66 69 75 ,6 Charts IM 21) Sella turcica before (left) and after treatment Measurement before 23 x 19 mm (790 sq mm) After 5 1/2 years 19 x 13 mm (387 sq mm)

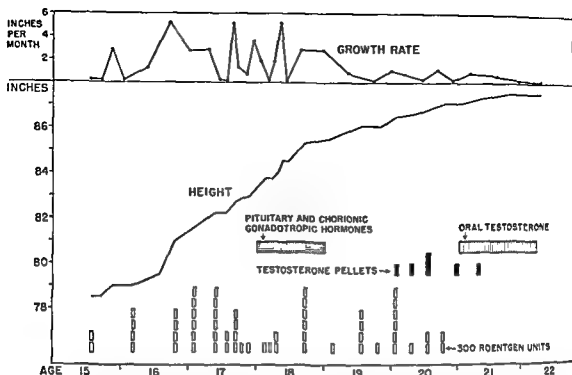


CHART 21 GROWTH AND TREATMENT CHART OF PITUITARY GIANT (See Protocol 9 XV Figs 61 62 65 66 69 73 75 76 Chart 18) Upper line represents the average growth rate per month (approximate) during the periods of time which followed roentgen treatment. Before treatment began the average growth rate per month over a 4 6 year period was 0.31 in (99 percentile growth curve of Burgess between 11 and 15 years is 0.21 in per month). It is to be noted that this method of charting appears to depict growth changes dramatically although it is more sensitive to errors in recording height. The effect of roentgen therapy we believe, clearly shown.

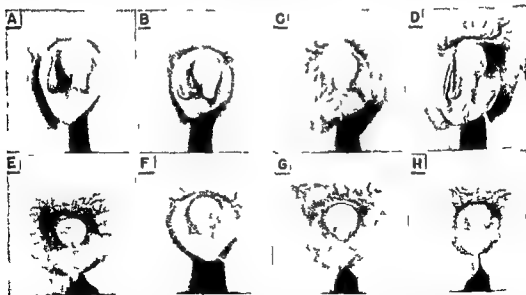


FIG 75 PITUITARY GIGANTISM (See Protocol 9 XV Figs 61 62 65 66 69 73 76 Charts 18 21) Genitalia before and after chorionic and pituitary gonadotropic therapy (330 000 units 11 months) regression after 1 year and return of pubic hair and other secondary sex characteristics after testosterone pellet implantation (A to E) At onset to end of gonadotropic and chorionic hormone therapy (F) One year after cessation of above therapy (G) After 16 months of testosterone therapy. There was only a slight increase in size of testes (H) About 8 months after discontinuing testosterone

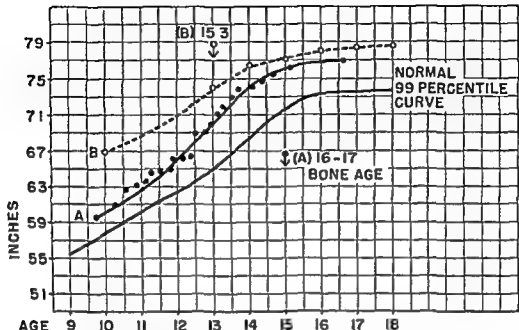


CHART 20 UNUSUAL TALLNESS (See Protocol 9 XVIII Figs 71 72) Growth curves of two unusually tall boys (atavistic gigantism) compared with the 99 normal percentile curve (Burgess) (A) Birth length 21 in Weight 9 lbs 5 oz Parents not tall Grandfather 76 in Bone age at 15 advanced (B) Birth weight 9 lbs 14 oz Parents and Siblings under 70 in Curve tapers off slower than curve A Bone age at 13 was 15 and growth continued for 4 years thereafter These curves illustrate variability of growth and the difficulty in estimating final height in a given case Puberty began at approximately the same time in both cases pubic hair present in both at 13 years of age



FIG 74 PITUITARY GIGANTISM (See Protocol 9 XVI Figs 63 67 68) A microscopic section of the spongy overgrowth of the skull which was removed during operation Note numerous osteo blasts and osteoclasts on surface of compact bone Fibrotic areas stain lightly (x 172)

SECTION 10
ACROMEGALY
 (Marie s Malady⁹⁰)

I DEFINITION	Acromegaly is a disease characterized by postpuberal by perfunction of pituitary acidophilic cells causing progressive increase in the size of acral parts of the body
II APPEARANCE	Marked hypertrophy of all facial components, with big pawlike hands and feet, with or without spinal deformities height may be above normal, 'apelike' (see photos)
III AGE	Onset late in second decade or thereafter, 50 per cent begin in third decade ¹¹⁶
IV SEX	Males and females equally affected ¹¹⁶
V MENTAL DEVIATIONS	
A INTELLIGENCE	Variable
B RESPONSIVENESS	Often irritable, later irascible morose, apathetic, stuporous slow
C OTHER ABNORMALITIES	Memory usually not altered, introspective, may have psychoses
VI PHYSICAL STATUS	
A NUTRITION	Good
1 Weight	Normal or slightly increased unless complicated by severe hyperthyroidism
2 Fat distribution	Normal
B HEIGHT	Often normal depends on age of onset curvature of the spine decreases stature
C EXTREMITIES	
1 Upper	Proportionate to body size but seem small in comparison with hands joints are all big
a Hands	Pawlike enlarged in circumference but not lengthened grasp decreased (see Fig 79)
b Fingers	Normal length but appear short because of increased circumference ends bluntly rounded may show hypertrophic arthritis
■ Span	Not increased, unless dorsal round back or kyphosis ■ found
2 Lower	Proportionate to body size, joints enlarged, especially knees may be bowlegged
a Feet	Pawlike big (changes similar to hands), tendency to be flat plantar surface has deep folds and hypertrophied pads
b Toes	May be rounded thickened
D SPINE	Dorsal Lyphosis lordosis and/or scoliosis may eventually develop

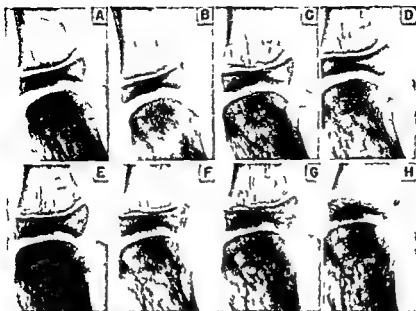


FIG 16 PITUITARY GIGANTISM (See Protocol 9 \V Figs 61 62 65 66 69 74 75 Charts 18 21) Epiphyses of first metacarpal phalangeal joint (A B C) During roentgen therapy of pituitary gland only for 28 month period (D E) During roentgen therapy plus chorionic and pituitary gonadotropic injections twenty eighth to thirty seventh months (F) Six months after cessation of treatment thirty seventh to forty third months (G) At beginning of testosterone therapy (H) Sixteen months after institution of testosterone therapy and cessation of longitudinal growth Note that epiphyses in A and D are essentially the same after 2½ years of roentgen treatment alone and that closure appeared to begin after hormone therapy and was complete in 2 years



FIG 77 PITUITARY GIANT Typical pituitary giant with his father mother brothers and sisters Height 108 in Growth curve shown on Chart 18

- b Teeth Widely spaced, dental caries, loose, appear big, change of bite¹⁻⁶
- c Larynx (voice) Hypertrophy of larynx and vocal cords, voice deep in both sexes unless secondary gonadal atrophy occurs prominence of thyroid cartilage
- G NECK
- 1 General Short or long but always thick and heavy, sunken between rounded shoulders
- 2 Thyroid (see Fig 82) May be palpable, hyperplastic or adenomatous^{33 34 37 0}
- 3 Glands Submaxillary and salivary are occasionally palpable
- H CHEST
- Normal or large in size with anteroposterior diameter greater in proportion to lateral, kyphosis and/or scoliosis and/or lordosis, "hunchback" appearance sternum may be protuberant, clavicles prominent, interspaces broadened and huge ribs
- I HEART AND PERIPHERAL VESSELS
- 1 Heart Normal or may be enlarged¹¹³
- 2 Rate and rhythm Normal or tachycardia with or without hyperthyroidism, may have auricular fibrillation
- 3 Blood pressure Variable elevated in 10 per cent⁶⁰ less than 120 systolic in 30 per cent^{70 116}
- 4 Peripheral arteries and veins From normal to thickening and marked sclerosis of vessels veins are increased in size, varicosities common
- 5 Vasomotor Flushed
- J BREASTS
- 1 Male Lactation may be present, prominent, erectile nipples^{13 3 123}
- 2 Female Overgrowth or atrophy, may be lactating in absence of pregnancy^{27 9 113 135}
- K ABDOMEN
- Pendulous
- 1 Liver Occasionally enlarged, may be due in part to associated diabetes or congestive heart failure--^{55 118}
- 2 Spleen Any size
- 3 Hernia Not common
- 4 Tumor None if kidneys sufficiently hypertrophied may be palpated
- L GENITALIA
- 1 Male
- a Penis Enlarged proportionately
- b Testes Normal
- c Prostate Normal⁷⁷
- 2 Female
- a External Normal or enlarged
- b Internal Variable depending on stage of the disease often atrophic or infantile as expected with menopause
- M NEUROMUSCULAR
- 1 Muscles Vary in development, depending on period of the disease, may be very muscular soft, flabby or atrophic
- 2 Gait Normal or slow and cumbersome
- 3 Body movements Normal or may be clumsy forward motion of spine limited

E. INTEGUMENT

1 General

a Texture

Marked hypertrophy of all subcutaneous tissues later atrophic changes deep folds at nasolabial area forehead scalp and shoulders also hands and feet have coarse heavy pads, flesh overhangs nails nail bed not widened Enlarged pores firm consistency but with subcutaneous softness

b Temperature

Increased in extremities may be from 2° to 3° above normal with or without hyperthyroidism due to increased vascularity of acral parts body temperature may be subnormal

c Moisture

Usually excessive often offensive in later stage, absent

d Eruptions

Acne warts, moles infection of apocrine glands mollus cum fibrosum, lipoma xanthomata

e Pigmentation

Generalized or localized yellow or brown tinge occasionally vitiligo reported after estrogen therapy¹⁰⁸

f Color

Sallow, hands may be cyanosed at metacarpals because of extreme thickening of skin pallor late in disease¹⁰

2 Hair

a Head

Thick coarse rarely sparse and thin

b Facial

Males may have an increased amount females show excessive growth on chin and upper lip (see Fig 80)

c Axillary

May be increased

d Pubic

Normal or increased, scant rarely⁷³

e Body

Furry thick growth on limbs and trunk in some cases or may have hypotrichosis

F HEAD (see Figs 79-85)

1 Shape and size

Increased size, especially in circumference narrow and recessive forehead, prominent external protuberance of occiput malar bones conspicuous variable prognathism⁷⁰ face elongated and oval head may fall forward on chest Melancholic, emotionless passive stolid

2 Facial expression

3 Eyes

a General

Deeply seated rarely exophthalmos^{61 148} eyeballs reported enlarged eyelids thick eyelashes normal may have oculomotor palsy or palsies normal accommodation occasionally nystagmus increased lacrimation (if associated with hyperthyroidism see 26 VI A) conjunctivitis

b Fundi

May have optic atrophy or some optic edema (rare)

c Visual

(1) Fields

Variable defects may occur usually bitemporal hemia chromatopsia and/or central scotomata may precede optic atrophy (see Table 7 and Fig 91)⁶

(2) Acuity

Normal slight amblyopia or complete blindness

4 Ears and nose

Marked increase in length and width of nose with large nostrils alae thick mucous membranes and septum hypertrophied impaired sense of smell occasionally and/or deafness ears may be very large (see Fig 81)

5 Mouth and throat

a General

Marked hypertrophy and thickening of soft palate uvula and lips lower one may be everted tongue increased in size at times protrudes papillae are hypertrophied

D FUNCTION TESTS

1 Tolerance (see Chart 22)

a Glucose

Inconstant results, large percentage show decreased tolerance, rarely 'Houssay dog' phenomena (see 2 VI C 15, 10 V C 103 I D 1)^{3 14 17 22 33 50 53 58 67 75 76 83 85 91 9 96 100 106 1 1 1 6 III 125 137 138 147 149 151}

b Glucose insulin

Inconstant results^{47 137}

c Insulin

Variable results, hypoglycemic levels rarely^{33 83 136 187}

d Galactose

Normal or low in late stages¹

e Iodine

As in hyperthyroidism if present

f Creatine

Higher than normal, curve rises then tends to fall in 3 hrs^{5 127}

2 Adrenal water

No data, may be positive in "burnt out" cases⁷⁷

3 Salt deprivation

Normal or may be positive in advanced cases^{136 197}

4 Balance

a Nitrogen

Negative but this must be considered from point of view of active acromegaly and associated secondary endocrine activity, reported slightly positive^{1 III 16 3 40 48 67 III 81 10 100 11 1 4 13 140}

b Calcium

Negative^{14 16 40 48 10 100 112 1 6 127 130 140} (question of thyroid or parathyroid influence^{1 III 81}), not related to basal metabolic rate, usually follows nitrogen balance, could be positive

c Phosphorus

May be negative or positive^{8 14 16 40 III 105 100 11 1 4 130 140}

d Potassium

Normal^{68 105}

5 Renal

a Phenolsulfonphthalein

Normal^{67 76}

b Urea clearance

May be upper limit of normal¹¹

E MISCELLANEOUS TESTS

1 Basal metabolic rate

Elevated in 70 per cent of cases (not always associated with enlarged thyroid) (see 2 VI B 16)^{14 0 116 156 151}

2 Circulation time

Normal or increased if basal metabolic rate is elevated

3 Sedimentation rate

Normal

4 Specific dynamic action of protein

Normal³

5 Gastric analysis

Normal hypochlorhydria or achlorhydria^{51 85}

6 Electrocardiogram

Normal or degenerative changes^{1 III 151}

7 Spinal fluid

Normal¹⁵¹

8 Fecal excretion

■ Calcium

Normal¹⁴

b Phosphorus

Normal¹⁴

c Creatine

Normal^{123-1 7}

F URINARY HORMONE ASSAYS

1 Follicle stimulating hormone

Generally reduced (blood and urine) from pressure of tumor but depends theoretically on ability of basophilic cells to function if local pressure exists^{1 22 20 55 73 79 81 83 94 95 100 144} may be present at menopause in some cases roentgen therapy may decrease output

2 Luteinizing hormone

Active case may have increased amounts ■ stationary cases no increase (blood and urine)*

3 Estrogens

Variable but should follow activity of basophilic cells, as above⁶⁹

* Transplant of eosinophilic adenoma of acromegalic giant failed to produce any change in ovaries of mice
220

- | | |
|----------------|--|
| 4 Tremor | May be present with unilateral extension of tumor or hyperthyroidism |
| 5 Paresthesias | May occur |
| 6 Reflexes | Variable may show hemiplegia or paraplegia |
| N SPEECH | Normal or large tongue may interfere with distinct and free articulation |

VII LABORATORY DATA

A URINE

- | | |
|--------------------|---|
| 1 General | Normal volume variable |
| 2 Special analyses | |
| a Sugar | May be present without diabetes |
| b Albumin | May be present |
| c Nitrogen | Normal or decreased excretion (see below) |
| d Uric acid | Increased output (endogenous) ⁸¹ |
| e Creatine | Increased excretion but variable ^{1 81 122-128} |
| f Creatinine | As for creatine |
| g Calcium | Increased output (dependent on activity of disease) ^{1 8}
11 18 47 83 103 109 11 17 140 147 |
| h Phosphorus | Increased output ^{10 40 49 81 80 109 11 1 140} |
| i Chloride | Increased ^{99 100} |
| j Iodine | Normal or in excess if basal metabolic rate is elevated ^{70 85} |
| k Magnesium | Variable ^{16 45} |

B HEMATOLOGY

- | | |
|---------------------|---|
| 1 Red blood cells | Normal or reduced in late stages ^{23 4 76 151 15} |
| 2 Hemoglobin | Normal or low with progression of disease |
| 3 White blood cells | Normal or decreased in advanced cases |
| 4 Differential | Monocytosis slight increase in eosinophils and/or lymphocytosis |

C BLOOD CHEMICAL ANALYSES

- | | |
|-----------------------|--|
| 1 Sugar | Variable often diabetic level (12%) ^{70 82 6 93 135 144 151} |
| 2 Nonprotein nitrogen | Generally normal ^{14 28 47} may be increased ^{78 83 1 0} |
| a Urea nitrogen | As for nonprotein nitrogen ^{78 140 151} |
| 3 Protein | Normal or upper normal ^{150 101 1 0} |
| a Albumin | Normal |
| b Globulin | Normal |
| c A/G ratio | Normal |
| 4 Uric acid | May be increased occasionally ^{73 76 80 1 0} |
| 5 Cholesterol | Variable may be very low even if basal metabolic rate is not elevated ^{1 6 177 136} |
| 6 Sodium | Low normal ¹³³ |
| 7 Potassium | Low normal ¹³³ |
| 8 Calcium | Normal, may be decreased ^{1 14 5 81 83 1 1 120 127 130 135 147 140} |
| 9 Phosphorus | Normal or increased in active phase of disease ^{71 81 83 119 120 125 136 147} |
| 10 Phosphatase | Normal ^{1 81 120 135 147} |
| 11 Chlorides | Normal ^{107 78 176} |
| 12 Iodine | Normal or increased ^{150 114} |
| 13 Creatine | Increased ²⁶ |
| 14 Creatinine | Variable ^{20 78 85} |

IX ETIOLOGY

A UNKNOWN

II HEREDITARY OR CONGENITAL—Occurrence in members of same family has been reported^{10 63}X PATHOLOGY^{7 23 27 33 34 42 55 58 72 80 100 133 147}

A GROSS

1 Comment—generalized splanchnomegaly and adenomas of all organs, but at times within normal range

2 Pituitary (see 2 IX, B 12 b)

a Normal^{10 38}

b Hyperplasia

c Adenoma

(1) Acidophilic

(2) Outside of sella in path of Rathke's pouch (rarely)⁴¹

d Sarcoma¹¹⁷

e Cystic degeneration

f Cancer (unusual)¹³³

3 Thyroid⁶⁴

a Normal

b Hypertrophy

(1) Unilateral

(2) General

c Atrophy

d Hyperplasia

e Adenoma

(1) Single

(2) Multiple

f Colloid degeneration

g Absent on one side

4 Parathyroids

a Hypertrophy

b Adenoma

(1) Single

(2) Multiple

5 Adrenals

a Normal¹⁴⁷

b Cortical adenomas—common

6 Testes

a Normal^{110r 133}

b Hypertrophy¹³³

c Atrophy^{31 55 129 141}

7 Ovaries

a Atrophy^{5 4r}

b Hypertrophic changes occasionally

■ 141

8 Pancreas

a Normal

b As in diabetes mellitus (in cases with glycosuria and hyperglycemia)⁷³

(1) Fibrosis

(2) Atrophy

(3) Hypertrophy

(4) Fatty degeneration

(5) Suppuration

(6) Interstitial hemorrhages

(7) Islet cells may be

(a) Atrophic

(b) Hyperplastic

(c) Absent

c Adenoma

d Enlarged

9 Thymus

a Present^{10 63}

b Absent⁶⁴

c Enormous^{2 5 6 116}

10 Liver

a Normal

b Hypertrophy (5 900 to 6,200 Gm)¹¹¹

c Fatty degeneration

d Chronic congestion

e Hypertrophic cirrhosis

11 Heart

a Normal

b Hypertrophy (1,275 Gm)¹¹³

c Atrophy

d Endocarditis

e Valvular disease

f Coronary involvement

12 Kidneys

a Normal

b Enlarged

13 Spleen

a Normal

b Enlarged

14 Prostate

a Normal

b Enlarged

15 Bones^{71 4 43 80 139 147}

a Heavy (see Fig 87)

b Thick increased in transverse diameter

c Long ones—wide

d Muscular attachments and ridges are prominent

e Surfaces roughened

f Hyperostoses

g Exostoses

h Arthritic changes (periosteal ossification with pathologic proliferation of cartilage)

i Ankylosis (see Fig 90)

4 Pregnanolol	If menses exist
5 17 ketosteroids	Usually normal or low but could be increased ^{1 2 8 41 50} 67 3 81 83 100 101 104 118 1 1 14 146
6 11 oxysteroids	Normal or slightly increased ^{118 116}
7 Aschheim Zondek	Negative unless pregnant which is possible, ⁷⁰ occasionally positive in males and females ⁷²
8 Thyrotropic hormone	Increased (blood also) ^{46 111 131}
G BIOPSY	
1 Endometrial	Often atrophic but variable depending on ovarian activity
2 Testicular	See microscopic pathology
H VAGINAL SMEAR	Normal or atrophic
I SEMEN ANALYSIS	Normal or decreased count ^{1 83}

VIII ROENTGENOGRAPHIC FINDINGS (see Figs 86 to 90)

A SKULL	
1 Cranial vault	Irregularly thickened prominent occipital protuberance malar and zygomatic bones hyperostoses, ^{70 151} osseous hypertrophy (see Protocol 9 XVI)
2 Sella turcica	Enlarged or eroded in over 90 per cent (although only 80% reported by Vaughn ¹¹⁵) may be unilateral, often extension into sphenoid sinus and nasopharynx (see 2 XIV G and Table 7)
3 Mandible	Slight to marked prognathism, may have subluxation
4 Sinuses	Usually enlarged and wide
5 Teeth	Widely spaced due to enlarged jaw and heaping up of alveolar arches ⁵⁰
B EPIPHYSEAL STATUS (bone age)	Closed epiphyses are broadened
C LONG BONES	
1 General	Occasionally increased in length at epiphyseal extremity, enlargement of head tuberosities muscular attachments spines and exostoses are common long bones widened may show hypertrophic arthritis periosteal ossification with pathologic proliferation of cartilage cystic degeneration ^{1 4 43 80 129 147}
2 Carpals	Increased in size and roughened surfaces
3 Tarsals	Enlarged less evident changes than with the carpals
4 Phalanges (terminal)	Often tufted however not diagnostic until late in disease
D VERTEBRAE	Hypertrophy and later ankylosis degenerative arthritic changes anteroposterior width increased 80 per cent of cases show spinal changes ^{7 4 43 147}
E BONE TEXTURE	Coarse spur formation advanced cases osteoporotic atrophy and rarefaction of cancellated bone vascular channels visible and large ² cartilage may be calcified
F MISCELLANEOUS ¹³⁹	
1 Sternum	Hypertrophied protuberant
2 Scapulae	Normal or enlarged
3 Clavicles	Big thickened broad
4 Pelvis	Normal or enlarged
5 Patellae	Increased in all diameters
6 Kidneys	Normal size or enlarged stones may be noted ⁷¹
7 Stomach	More or less enlarged in most cases

IX ETIOLOGY

A UNKNOWN

B HEREDITARY OR CONGENITAL—Occurrence in members of same family has been reported^{19 29}X PATHOLOGY^{7 23 27 28, 31 4 5 58 7}
■ 1, 2 133 147

A GROSS

1 Comment—generalized splanchnomegaly and adenomas of all organs, but at times within normal range

2 Pituitary (see 2 I \ II 12 b)

a Normal^{10 38}

b Hyperplasia

■ Adenoma

(1) Acidophilic

(2) Outside of sella in path of Rathke's pouch (rarely)⁴¹d Sarcoma¹¹⁷

e Cystic degeneration

f Cancer (unusual)¹³³3 Thyroid⁴

a Normal

b Hypertrophy

(1) Unilateral

(2) General

c Atrophy

d Hyperplasia

■ Adenoma

(1) Single

(2) Multiple

f Colloid degeneration

g Absent on one side

4 Parathyroids

■ Hypertrophy

b Adenoma

(1) Single

(2) Multiple

5 Adrenals

■ Normal⁶⁷

b Cortical adenomas—common

6 Testes

a Normal^{100 133}b Hypertrophy¹³³c Atrophy^{31 5 129 141}

7 Ovaries

a Atrophy^{5 47}b Hypertrophic changes occasionally^{58 141}

8 Pancreas

a Normal

b As in diabetes mellitus (in cases with glycosuria and hyperglycemia)⁷³

(1) Fibrosis

(2) Atrophy

(3) Hypertrophy

(4) Fatty degeneration

(5) Suppuration

(6) Interstitial hemorrhages

(7) Islet cells may be

(a) Atrophic

(b) Hyperplastic

(c) Absent

■ Adenoma

d Enlarged

9 Thymus

a Present^{19 58}b Absent⁶⁴c Enormous^{29 53 62, 110}

10 Liver

■ Normal

b Hypertrophy (5,900 to 6,200 Gm)¹¹⁴

c Fatty degeneration

d Chronic congestion

■ Hypertrophic cirrhosis

11 Heart

a Normal

b Hypertrophy (1,275 Gm)¹¹³

c Atrophy

d Endocarditis

e Valvular disease

f Coronary involvement

12 Kidneys

a Normal

b Enlarged

13 Spleen

a Normal

b Enlarged

14 Prostate

a Normal

b Enlarged

15 Bones^{71 4- 43 80 139 147}

a Heavy (see Fig 87)

b Thick increased in transverse diameter

c Long ones—wide

d Muscular attachments and ridges are prominent

e Surfaces roughened

f Hyperostoses

g Exostoses

h Arthritic changes (periosteal ossification with pathologic proliferation of cartilage)

i Ankylosis (see Fig 90)

- j Cystic degeneration
- k Cartilaginous ossification

B MICROSCOPIC^{9 10 33 34 47 7* 88}

- 1 Pituitary (duration of disease and treatment may change its cellular structure) (see 2 IX B 12 b)
 - a Acidophilic cells
 - (1) Hyperplasia usually in proportion to degree of activity, but picture is variable^{10 88 116}
 - (2) No special arrangement
 - b Tumor presses against remaining cells
 - c Few blood vessels present
 - d Adenoma may be encapsulated
 - Mixed tumors nondescript
- 2 Testes
 - Seminiferous tubules^{116 133}
 - (1) Hypertrophic
 - (2) Atrophic
 - (3) Fibrotic
 - b Interstitial cells^{116 133}
 - (1) Normal
 - (2) Hypertrophic
 - (3) Atrophic
 - c Spermatogenesis
 - (1) Normal^{1 83}
 - (2) Absent¹³³

- 3 Retention, for tissue synthesis, of
 - a Nitrogen
 - b Phosphorus

D GONADOTROPIC HORMONES

- 1 FSH may be
 - a Decreased
 - b Increased
- 2 LH is
 - a Excessive (probably) in early cases causing increased (?) libido in males
 - b Decreased or absent due to pressure from tumor producing amenorrhea (against acidophilic origin of LH)

E THYROTROPIN

- 1 Excessive amount in many patients causes greater energy requirements (through thyroid gland)
- 2 Caloric intake must be adequate and if insufficient, fat is burned in excess
- 3 Retardation of glycogen formation and hyperglycemia may be due to hypersecretion of thyroid hormone

F ADRENOCORTICOTROPIN

- 1 Adrenals are stimulated to a variable excess in the production of their hormones (see 39 VI B)
- 2 Adrenocortical carbohydrate (S') hormones cause an increased breakdown of protein into glucose
 - a Sufficient amounts may counteract to a certain degree the effects of
 - (1) Growth hormone
 - (2) Insulin
 - (3) 'N' hormone
 - b Excessive quantities produce a 'weak acromegalic (Albright)
- 3 Adrenocortical 'N' hormone may increase resulting in a 'strong acromegalic' if quantity is greater than the S' hormones (unconfirmed)
- 4 17 ketosteroids are elevated in some cases
- 5 Hair growth promoting hormones may be increased (doubtful if also androgenic)

G DIABETOGENIC FACTOR

- 1 Compensatory increase in insulin secretion (question of growth hormone effect) (see 2 VI B 7)
- 2 Exhaustion of islets of Langerhans may result eventually with production of insulin deficient hyperglycemia (true diabetes)

XI PATHOLOGIC PHYSIOLOGY

A INTRODUCTION

- 1 It seems likely that some cases of acromegaly may be associated with an excess of other pituitary hormones besides the growth hormone
- 2 More recent studies on the pure growth hormone suggest that it has little effect on other endocrine glands⁹⁰

B EXPANDING TUMOR

- 1 Headache may be due to
 - a Local pressure
 - b Hormones alone this is largely conjectural
- 2 If tumor is confined within the capsule pressure may decrease the secretion of various hormones
- 3 Optic nerve damage may be produced by extension of tumor beyond sella

C GROWTH HORMONE

- 1 Overproduction occurs affecting all tissues
- 2 Protein is spared as a source of energy

IX ETIOLOGY

A UNKNOWN

B HEREDITARY OR CONGENITAL—Occurrence in members of same family has been reported^{19 89}X PATHOLOGY^{7 23 27 3 31 4 53 58 72 80 120 133 147}

A GROSS

1 Comment—generalized splanchnomegaly and adenomas of all organs, but at times within normal range

2 Pituitary (see 2 IX B 12 b)

a Normal^{10 38}

b Hyperplasia

c Adenoma

(1) Acidophilic

(2) Outside of sella in path of Rathke's pouch (rarely)⁴¹

d Sarcoma¹¹⁷

e Cystic degeneration

f Cancer (unusual)¹⁵³

3 Thyroid⁵⁴

a Normal

b Hypertrophy

(1) Unilateral

(2) General

c Atrophy

d Hyperplasia

e Adenoma

(1) Single

(2) Multiple

f Colloid degeneration

■ Absent on one side

4 Parathyroids

a Hypertrophy

b Adenoma

(1) Single

(2) Multiple

5 Adrenals

a Normal⁴⁷

b Cortical adenomas—common

6 Testes

a Normal^{100 133}

b Hypertrophy¹³³

c Atrophy^{31 53 129 141}

7 Ovaries

a Atrophy^{25 47}

b Hypertrophic changes occasionally^{83 141}

8 Pancreas

■ Normal

b As in diabetes mellitus (in cases with glycosuria and hyperglycemia)⁷³

(1) Fibrosis

(2) Atrophy

(3) Hypertrophy

(4) Fatty degeneration

(5) Suppuration

(6) Interstitial hemorrhages

(7) Islet cells may be

(a) Atrophic

(b) Hyperplastic

(c) Absent

■ Adenoma

d Enlarged

9 Thymus

a Present^{19 83}

b Absent⁶⁴

■ Enormous^{3 33 41 116}

10 Liver

a Normal

b Hypertrophy (5 900 to 6,200 Gm)¹¹⁶

c Fatty degeneration

d Chronic congestion

e Hypertrophic cirrhosis

11 Heart

a Normal

b Hypertrophy (1 275 Gm)¹¹³

c Atrophy

d Endocarditis

e Valvular disease

f Coronary involvement

12 Kidneys

a Normal

b Enlarged

13 Spleen

a Normal

b Enlarged

14 Prostate

a Normal

b Enlarged

15 Bones^{21 42 43 80 139 147}

a Heavy (see Fig 87)

b Thick increased in transverse diameter

■ Long ones—wide

d Muscular attachments and ridges are prominent

■ Surfaces roughened

f Hyperostoses

g Exostoses

h Arthritic changes (periosteal ossification with pathologic proliferation of cartilage)

i Ankylosis (see Fig 90)

- j Cystic degeneration
- k Cartilaginous ossification

B MICROSCOPIC⁹ 10 33 39 47 7 88

- 1 Pituitary (duration of disease and treatment may change its cellular structure) (see 2 IX II 12 b)

a Acidophilic cells

- (1) Hyperplasia usually in proportion to degree of activity, but picture is variable^{10 86 110}
- (2) No special arrangement

b Tumor presses against remaining cells

- Few blood vessels present
- d Adenoma may be encapsulated
- Mixed tumors nondecript

2 Testes

a Seminiferous tubules^{110 113}

- (1) Hypertrophic
- (2) Atrophic
- (3) Fibrotic

b Interstitial cells^{110 113}

- (1) Normal
- (2) Hypertrophic
- (3) Atrophic

c Spermatogenesis

- (1) Normal^{1 80}
- (2) Absent¹¹³

3 Retention, for tissue synthesis of

- a Nitrogen
- b Phosphorus

D GONADOTROPIC HORMONES

1 FSH may be

- a Decreased
- b Increased

2 LH is

- a Excessive (probably) in early cases causing increased (?) libido in males
- b Decreased or absent due to pressure from tumor producing amenorrhea (against acidophilic origin of LH)

E THYROTROPIC

1 Excessive amount in many patients causes greater energy requirements (through thyroid gland)

2 Caloric intake must be adequate and, if insufficient, fat is burned in excess

3 Retardation of glycogen formation and hyperglycemia may be due to hypersecretion of thyroid hormone

F ADRENOCORTICOTROPIC

1 Adrenals are stimulated to a variable excess in the production of their hormones (see 39 VI B)

2 Adrenocortical carbohydrate (S') hormones cause an increased breakdown of protein into glucose

a Sufficient amounts may counteract to a certain degree the effects of

- (1) Growth hormone
- (2) Insulin
- (3) "N" hormone

b Excessive quantities produce a 'weak acromegalic' (Albright)

3 Adrenocortical 'N' hormone may in create resulting in a 'strong acromegalic' if quantity is greater than the 'S' hormones (unconfirmed)

4 17 keto steroids are elevated in some cases

5 Hair growth promoting hormones may be increased (doubtful if also androgenic)

G DIABETOGENIC FACTOR

1 Compensatory increase in insulin secretion (question of growth hormone effect) (see 2 VI B 7)

2 Exhaustion of islets of Langerhans may result eventually with production of insulin deficient hyperglycemia (true diabetes)

XI PATHOLOGIC PHYSIOLOGY

A INTRODUCTION

1 It seems likely that some cases of acromegaly may be associated with an excess of other pituitary hormones besides the growth hormone

2 More recent studies on the pure growth hormone suggest that it has little effect on other endocrine glands⁸⁰

B EXPANDING TUMOR

1 Headache may be due to

- a Local pressure
- b Hormones alone this is largely conjectural

2 If tumor is confined within the capsule pressure may decrease the secretion of various hormones

3 Optic nerve damage may be produced by extension of tumor beyond sella

C GROWTH HORMONE

1 Overproduction occurs affecting all tissues

2 Protein is spared as a source of energy

H PARATHYROID STIMULATION (parathyroid hormone (?) and/or other causes)

- 1 Calcium metabolism stimulated
 - a Excretion increased
 - b Balance may be negative even with a positive nitrogen balance due to unknown factors
- 2 Nephrolithiasis is common

XII SYMPTOMATOLOGY^{19 7 8 70} ^{07 116}

A EXPANSION OR EXTENSION OF TUMOR WITH INCREASED INTRACRANIAL PRESSURE

- 1 Neuromuscular complaints
 - a Headaches⁷⁰
 - (1) Location not consistent
 - (2) Most frequently
 - (a) Frontal
 - (b) Temporal
 - (c) Supraorbital
 - b Paresthesias
 - c Pains or burning in extremities
 - d Thermal sensitivity
 - e Weakness (may have sudden fatigue)
 - f Hemiplegia
 - g Paraplegia
 - h Somnolence
 - i Lethargy (often marked)
 - j Insomnia
 - k Failing memory
 - l Depression
- m Vertigo
- n Neuralgia—facial ache⁷⁷ may occur⁹⁷
- o Lack of equilibrium
- p Convulsive seizures
 - (1) General
 - (2) Focal
- q Uncinate gyrus seizures are characterized by olfactory and gustatory auras without epileptiform convulsions⁷⁷
- 2 Special senses are affected
 - a Visual changes of variable degree
 - (1) Photophobia
 - (2) Conjunctivitis
 - (3) Strabismus
 - b Smell
 - (1) Impaired sometimes
 - (2) Epistaxis
 - (3) Periodic blood tinged and mucoid discharge

(4) Spinal fluid may leak with extension of tumor into sphenoid sinus

- c Taste may be involved
- d Ears
 - (1) Hearing impaired
 - (2) Tinnitus
 - (3) Intolerance to noise

B HORMONAL^{67 84}

- 1 Genito-urinary
 - a Impotence⁵
 - b Libido sexualis
 - (1) Lost
 - (2) Increased
 - c Menstrual periods
 - (1) Amenorrhea usually
 - (2) Irregular
 - (3) Prolonged
 - (4) Decreased
 - d Patient may become pregnant^{70 71}
^{110 134 149}
- 2 Progressive aggregate increase in size of
 - a Facial components
 - b Hands
 - c Feet

C GENERAL

- 1 Gastro intestinal
 - a Polyphagia
 - b Polydipsia
 - c Bulimia
- 2 Cardiorespiratory
 - a Dyspnea
 - b Palpitation
- 3 Arthritis (hypertrophic)¹⁴⁷

XIII DIAGNOSIS

A ROUTINE PROCEDURES

- 1 History—see symptomatology
- 2 Physical examination—check especially
 - a Weight
 - b Height
 - c Hands and feet enlargement
 - d Dorsal round back or kyphosis
 - e Perspiration
 - f Facial coarsening
 - g Prognathism
 - h Eyes
 - (1) Visual
 - (a) Fields
 - (b) Acuity
 - (2) Ocular fundi for
 - (a) Edema
 - (b) Atrophy

- j Cystic degeneration
- k Cartilaginous ossification

B MICROSCOPIC^{9 10 33 35 47 77 88}

- 1 Pituitary (duration of disease and treatment may change its cellular structure) (see 2 I\ B 12 b)
 - a Acidophilic cells
 - (1) Hyperplasia usually in proportion to degree of activity, but picture is variable^{10 88 116}
 - (2) No special arrangement
 - b Tumor presses against remaining cells
 - c Few blood vessels present
 - d Adenoma may be encapsulated
 - e Mixed tumors, nondescript
- 2 Testes
 - a Seminiferous tubules^{116 133}
 - (1) Hypertrophic
 - (2) Atrophic
 - (3) Fibrotic
 - b Interstitial cells^{116 133}
 - (1) Normal
 - (2) Hypertrophic
 - (3) Atrophic
 - c Spermatogenesis
 - (1) Normal^{1 83}
 - (2) Absent¹³³

- 3 Retention, for tissue synthesis of
 - a Nitrogen
 - b Phosphorus

D GONADOTROPIC HORMONES

- 1 FSH may be
 - a Decreased
 - b Increased
- 2 LH is
 - a Excessive (probably) in early cases causing increased (?) libido in males
 - b Decreased or absent due to pressure from tumor producing amenorrhea (against acidophilic origin of LH)

E THYROTROPIN

- 1 Excessive amount in many patients causes greater energy requirements (through thyroid gland)
- 2 Caloric intake must be adequate and, if insufficient fat is burned in excess
- 3 Retardation of glycogen formation and hyperglycemia may be due to hypersecretion of thyroid hormone

F ADRENOCORTICOTROPIN

- 1 Adrenals are stimulated to a variable excess in the production of their hormones (see 39 VI B)
- 2 Adrenocortical carbohydrate (S') hormones cause an increased breakdown of protein into glucose
 - a Sufficient amounts may counteract, to a certain degree the effects of
 - (1) Growth hormone
 - (2) Insulin
 - (3) N hormone
 - b Excessive quantities produce a weak acromegalic¹ (Albright)
- 3 Adrenocortical N hormone may increase resulting in a strong acromegalic if quantity is greater than the S hormones (unconfirmed)
- 4 17 ketosteroids are elevated in some cases
- 5 Hair growth promoting hormones may be increased (doubtful if also androgenic)

G DIABETOGENIC FACTOR

- 1 Compensatory increase in insulin secretion (question of growth hormone effect) (see 2 VI B 7)
- 2 Exhaustion of islets of Langerhans may result eventually with production of insulin deficient hyperglycemia (true diabetes)

XI PATHOLOGIC PHYSIOLOGY**A INTRODUCTION**

- 1 It seems likely that some cases of acromegaly may be associated with an excess of other pituitary hormones beside the growth hormone
- 2 More recent studies on the pure growth hormone suggest that it has little effect on other endocrine glands⁸⁰

B EXPANDING TUMOR

- 1 Headache may be due to
 - a Local pressure
 - b Hormones alone this is largely conjectural
- 2 If tumor is confined within the capsule pressure may decrease the secretion of various hormones
- 3 Optic nerve damage may be produced by extension of tumor beyond sella

C GROWTH HORMONE

- 1 Overproduction occurs affecting all tissues
- 2 Protein is spared as a source of energy

- 2 Other causes too numerous to list—see 61 II C, D

F HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

- 1 Skull—normal
- 2 Intrathoracic disease present
- 3 Cervicodorsal kyphosis
- 4 Hands and feet
 - a Shape—deformed
 - b Size—increased slightly
 - c Fingers
 - (1) Drumstick
 - (2) Curved nails
- 5 It is not likely to be confused with acromegaly

G ARTHRITIS (hypertrophic)

- 1 Typical arthritic findings without involvement of skull
- 2 No characteristic enlargement of
 - a Hands
 - b Feet
- 3 Acromegaly always should be considered

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A TUMOR CHANGES

- 1 Rupture of capsule is rare¹²³
 - a Pressure relieved
 - b Vision restored occasionally
- 2 Hemorrhage is not infrequent with a sudden loss of vision⁷¹
- 3 Extension
 - a Various neurologic effects
 - b Seepage of spinal fluid into nasopharynx from sphenoid sinus
- 4 Recurrence
 - a Despite all forms of therapy
 - b Even when apparently inactive

B HYPERTHYROIDISM (see 26 VIII)^{37 70 116}

- 1 Incidence—30 to 70 per cent
- 2 Onset—usually not early in disease
- 3 Characteristics
 - a Similar to toxic adenomatous goiter
 - b Exophthalmos—less frequent
 - c Basal metabolic rate increased extrathyroidal factor may be responsible⁵

C DIABETES MELLITUS (see 85 VIII)^{14 2-23 49 63 71 III 117}

- 1 Incidence
 - a Range—6 to 40 per cent^{6 18 22 72 70 93 118}

- b Hereditary tendency—21 per cent²²

2 Onset (average)

- a 9.5 years after acromegaly—
- b Age—38.8

3 Characteristics⁷⁷

- a Similar to ordinary diabetics in all features, except occasionally greater fluctuation in insulin requirement¹²
 - 23 III 75 76 78 11
- b More insulin resistant at times^{85 9}
 - 103 141 (estrogen may correct this¹)
- c Spontaneous recovery in some^{9 10}
 - 38 7 76
- d Thyroidectomy may reduce insulin requirement⁹⁷
 - Pituitary removal does not cure diabetes, but may be improved (see 2 VIC 15 Tables 101, p 1419 and 102, p 1426)⁹⁷
 - f Severity may indicate the degree of pituitary activity (?)^{10 118}

D CARDIOVASCULAR

1 Incidence

- a Up to 75 per cent reported to develop heart failure⁹⁹
- b One in 40 cases⁷¹

2 Characteristics⁹⁶

- a Size of heart is
 - (1) Not related to
 - (a) Intracranial pressure
 - (b) Hyperthyroidism
 - (c) Diabetes
 - (d) Hypertension
 - (2) Out of proportion to
 - (a) Muscular development
 - (b) Body physique
 - (3) Affected by minor factors as
 - (a) Chest deformity
 - (b) Displacement
- b Associated findings in some cases
 - (1) Angina pectoris
 - (2) Hypertension
 - (3) Nephritis (vascular)

E INTERCURRENT INFECTION

- 1 Any kind may develop^{70 118}
- 2 Bronchitis with emphysema

F RARE FINDINGS

- 1 Panhypopituitarism
- 2 Pituitary myxedema⁴⁵
- 3 Hyperparathyroidism⁷⁰
- 4 Addison's disease¹⁵
- 5 Leukemia⁷⁷
- 6 von Recklinghausen's disease¹⁹

- i Tongue hypertrophy
- j Thyroid size
- k Pulse rate
- l Blood pressure
- m Tremor
- 3 Laboratory data
 - a Urine for sugar
 - b Blood chemical analyses
 - (1) Sugar
 - (a) Fasting
 - (b) Two hrs after eating
 - (2) Phosphorus (serum fasting)
 - c Glucose tolerance test (2 hr)
 - d Basal metabolic rate
- 4 Roentgenograms
 - a Skull (stereoscopic) for secondary changes
 - (1) Sinus development
 - (2) Prognathism
 - (3) Intracranial pressure evidence (undue motting)
 - (4) Sellar size including area of lateral contours
 - (5) Both clinoids is to
 - (a) Separation
 - (b) Decalcification
 - (c) Interclinoid distance (dorsum floor)
 - (d) Other abnormalities
 - b Air or oxygen encephalograms for extension of tumor (see 2 VIII F 5)
 - c Hands
 - (1) Bone age
 - (2) Recording of size
- 5 Lumbar puncture for pressure readings
- B SUMMARY OF IMPORTANT CLINICAL DATA
 - 1 Irreducible minimum for diagnosis (active or inactive)
 - a Actual enlargement of acral parts must be established
 - b Hands and feet as well as facial alterations must have taken place simultaneously⁷¹
 - 2 Differentiation of active and inactive stages
 - a History to determine
 - (1) Onset
 - (2) Sweating
 - (3) Tachycardia
 - (4) Visual damage
 - (5) Menstrual change (unless at time of menopause)

- (a) Amenorrhea
- (b) Menorrhagia
- b Laboratory data
 - (1) Phosphorus (serum, fasting) is increased, based on repeated determinations in absence of other causes of hyperphosphatemia
 - (2) Basal metabolic rate may be elevated
 - (3) Glucose tolerance curve is often the diabetic type which may persist after inactivation of acromegalic process
- c Roentgenologic findings show progressive changes
- d Most of the above may be equivocal in which case diagnosis of activity may have to be postponed until sufficient evidence is collected
 - (1) If patient is under 30 years of age activity is likely to be present
 - (2) Elevation of fasting serum phosphorus of 4.5 mg % or more is adequate to confirm excessive growth hormone activity^{71 81 83 119}

XIV DIFFERENTIAL DIAGNOSIS

- 1 GIGANTISM—see § VIII
- B ACROMEGALOID CONSTITUTION (congenital prognathism without acromegaly—see Fig 92)⁷⁰
 - 1 Absence of other acromegalic
 - a Signs
 - b Symptoms
 - 2 Sella turcica not enlarged
- C HYPERTHYROIDISM AND DIABETES—Acromegaly should be considered in all cases (see 31)
- D FUGITIVE ACROMEGALY (see Fig 93)^{8 70}
 - 1 Patients with enlarged sella and clinical hypopituitarism in whom there are traces of previously active acromegaly
 - a Sinuses—prominent
 - b Hands and feet—large
 - c Acromegalic features—slight
 - 2 Mixed tumor probably containing chromophobe and chromophil cells, with the latter becoming inactive—see d(2) above
- E AMENORRHEA
 - 1 Often first symptom of acromegaly

- (a) Two months after first series has been completed
- (b) Tumor may
 - [1] Not be radiosensitive
 - [2] Be cystic, filled with fluid and blood
- (2) After second course or if rapid expansion of tumor occurs in spite of irradiation, surgery is warranted for such symptoms as progression of
 - (a) Visual field defects (gross)
 - (b) Sellar size
 - (c) Acromegalic features
- c For continued hyperthyroidism or severe diabetes—see below
- 4 Subsequent management
 - a Periodic observation every 3 months
 - b Judge by
 - (1) Headache
 - (a) Severity
 - (b) Recurrence
 - (2) Visual fields and/or acuity changes
 - (3) Acral parts enlarging
 - (4) Serum phosphorus if persistent or return of high levels
 - (5) Basal metabolic rate increasing
 - (6) Sella turcica increasing in size
 - c Visual improvement may occur up to 18 months after roentgen therapy¹³
 - d Activity in some cases may subside and remain stationary indefinitely
 - e Irradiation may have to be supplemented by surgical removal of tumor in an estimated 15 to 30 per cent⁷¹
- C SURGICAL
 - 1 Indications
 - a Progression of disease in spite of roentgen therapy over period of 6 to 12 months
 - b Visual loss suggests hemorrhage within tumor or cyst, if
 - (1) Sudden
 - (2) Marked
 - c Neurologic complications
 - d Extension of tumor as shown by oxygen encephalograms
 - 2 Procedures—see 13 VII^{27 30 35 71 137}
 - 3 Results
 - a Surgical outcome closely follows those obtained by roentgen therapy except that it may produce improvement when the latter
 - (1) Has failed to be effective
 - (2) Can no longer be used
 - b Hypopituitarism is more likely to occur
 - c Recurrence rate is reduced by post operative roentgen therapy
 - d Hyperthyroidism may not be relieved⁹⁷
- D HORMONAL^{1 56 67 71 81 11 190 138}
 - 1 Estrogens
 - a Indications
 - (1) Depression of excess growth hormone⁶⁷
 - (2) Amenorrhea—see below
 - (3) Menorrhagia—see below
 - (4) Persistent lactation—see below¹³⁸
 - b Dosage
 - (1) Oral
 - (a) Stilbestrol—0.5 to 5 m_g daily (gradually increase)
 - (b) Estrone (or conjugated estrogens)—0.6 to 6 mg daily
 - (2) Parenteral administration unnecessary
 - c Results
 - (1) No change in¹¹⁹
 - (a) Urinary
 - [1] Creatine
 - [2] Creatinine
 - (b) Nitrogen balance
 - (c) Basal metabolic rate
 - (2) Decrease in^{71 119}
 - (a) Calcium (marked)
 - [1] Urinary
 - [2] Fecal
 - (b) Phosphorus
 - [1] Serum
 - [2] Urinary
 - (c) FSH
 - (d) 17 ketosteroids
 - (3) Increase in phosphatase (serum)
 - (4) General effects
 - (a) Weight increased
 - (b) Decrease (by water displacement) in
 - [1] Hands
 - [2] Feet
 - (c) Testicular biopsy (if normal before therapy) shows that¹¹⁹

- 7 Syringomyelia^{18, 26}
- 8 Amyotrophic lateral sclerosis^{19, 20, 20a}
- 9 Glioma
- 10 Tabes¹⁹
- 11 Parkinson's disease²⁴
- 12 Granulosa-cell tumor^{23a}

XVI TREATMENT

A OBJECTIVES ARE RELIEF OF⁷¹

- 1 Tumor pressure and its effects from
 - a Expanding locally or extending to adjacent parts
 - (1) Headache
 - (2) Visual disturbance
 - (3) Mental or neurologic changes
 - (a) Convulsions
 - (b) Psychotic states
 - (c) Hemiplegia
 - b Expansion within the sella damaging the normal pituitary cells
 - (1) Impotence (males)
 - (2) Amenorrhea (females)
- 2 Hyperhormonal effects due to an over active tumor causing
 - a Enlargement of acral parts, diminution of tissue changes to normal may be possible in early cases
 - b Headache
 - c Hyperthyroidism
 - d Diabetes
 - e Cardiovascular symptoms
 - (1) Hypertension
 - (2) Congestive heart failure
 - f Bone alterations
 - (1) Arthritis—hypertrophic type
 - (2) Exostoses
 - (3) Kyphosis
 - (4) Orthopedic complications
- 3 Concomitant or late hypohormonal effects which may follow treatment or occur spontaneously
 - a Panhypopituitarism
 - b Selective pituitary hormonal deficiencies
 - (1) Gonadotropic
 - (2) Thyrotropic
 - (3) Adrenocorticotrophic

B ROENTGEN

- 1 Indications
 - a Active stage of disorder
 - b If the following visual changes providing they are not recent or sudden are found

- (1) Field defects
- (2) Diminished acuity

c Persistent

- (1) Amenorrhea
- (2) Galactorrhea
- (3) Headache

- 2 Procedure—over pituitary area (see 13 IX)^{14, 25, 29, 30, 71, 115, 149}

- 3 Results to be anticipated from first course of irradiation

a Improvement

- (1) Favorable outcome
 - (a) Normal catamenia returns in younger females
 - (b) Tissue swelling regresses in part at
 - [1] Tongue
 - [2] Palms of hands
 - (c) Headache
 - [1] Is relieved temporarily
 - [2] Recurs even if disorder appears arrested
 - (d) Visual defects are
 - [1] Improved
 - [2] Eliminated
 - (e) Acute edema may
 - [1] Induce mental abnormalities
 - [2] Cause further visual alteration
 - (f) Serum phosphorus decreased
 - (g) Glucose tolerance may improve
 - (h) Basal metabolic rate lowered
 - (i) Sellar size decreases in majority
 - (j) Hyperthyroidism of clinical significance may be ameliorated
 - (k) Other changes take place gradually
- (2) The above results indicate that the tumor is radiosensitive
- (3) Regardless of beneficial effects another series probably should be given within 4 months after initial program

b No improvement

- (1) Unless evidence of rapid extension of tumor (growth or hemorrhage) second series should be started

- b Doubtful value
 (1) Estrogens
 (2) Androgens
- 4 Menstrual disorders
 a Menorrhagia
 (1) Dosage
 (a) Oral
 [1] Stilbestrol—5 to 50 mg daily
 [2] Progesterone (buccal)—30 to 50 mg daily for 1 week, repeat in 21 days
 (b) Parenteral
 [1] Progesterone—10 to 20 mg daily for 1 week repeat in 21 days
 [2] Testosterone propionate—50 mg daily
 (2) Result—spontaneous recovery possible
- b Amenorrhea
 (1) Dosage
 (a) Oral
 [1] Stilbestrol—0.5 to 1.5 mg daily for 21 to 28 days
 [2] Progesterone (buccal)—30 to 50 mg daily during third week
 (b) Comment
 [1] Progesterone prescribed after stilbestrol if
 [a] Vaginal smear is estrogenic type
- [b] Bleeding does not follow
 [2] Estrogens in large and continued doses may increase size of tumor (see Protocol 10 VII, Fig 94, Chart 23)
 (c) Pituitary tumor may be temporarily more sensitive to roentgen therapy
 (d) Neither of these effects have been definitely proven
- 5 Persistent lactation
 a Dosage
 (1) Oral
 (a) Stilbestrol—1 to 5 mg daily
 (b) Methyltestosterone—20 to 50 mg daily
 (2) Parenteral—testosterone propionate, 25 mg daily
 b Comment—the above medications may be given if symptom is not arrested by roentgen or surgical therapy
- 6 Impotence—testosterone may be tried in the usual doses if there is no improvement with
 a Roentgen therapy
 b Surgery
- 7 Panhypopituitarism may develop with or without previous therapy for acromegaly
- 8 Lassitude and/or somnolence—benzedrine sulfate or similar preparations 10 to 30 mg orally daily

F RESULTS IN 20 CASES FOLLOWED FROM 3 TO 13 YEARS⁷¹

	NUMBER OF CASES
1 Roentgen therapy (initially)	16
■ Satisfactory and with no progression of disorder	14
b Unsuccessful and followed by surgery	2
(1) First case—favorable for 3 months then died of meningitis	
(2) Second patient—progression arrested catamenia returned but headache persisted	
2 Surgery as initial procedure with removal of tumor tissue and followed by roentgen therapy	2
■ Progression of disorder halted	
b Amenorrhea persisted in both (one a postmenopausal patient)	
3 Exploration of pituitary but tumor not removed (died later of leukemia)	1
4 Surgery for recurrence (improved after 2 operations but died following third recurrence inadequate roentgen therapy)	1

- [1] Leydig cells are
 - [a] Absent
 - [b] Decreased
- [2] Tubules
 - [a] Few remain
 - [b] Spermatogenesis decreased
 - [c] Basement membrane may be collagenous

- d Objections (testosterone may overcome these effects⁸¹—see below)
 - (1) Breast enlargement possible⁷¹
 - (2) Testicular atrophy¹¹⁹
 - (3) Pituitary tumor may increase in size (see Protocol 10 \V\)⁷¹

2 Testosterone^{71 86}

a Indications

- (1) Asthenia of severe degree
- (2) Panhypopituitarism which may occur subsequently in burnt out cases
- (3) Trial in patients with loss of libido
- (4) Menorrhagia—see below
- (5) Neutralization of undesirable effects from estrogen therapy

b Dosage

- (1) Oral or buccal—methyltestosterone 50 to 100 mg daily
- (2) Intramuscular—testosterone propionate 100 mg or more weekly
- (3) Pellets—testosterone 200 to 400 mg every 2 or 3 months as indicated by rate of absorption

E. COMPLICATIONS

1 Hyperthyroidism (see 26 \VI)

a Mild—await result of

- (1) Roentgen therapy
- (2) Surgery (if required)

b Severe

- (1) Preparation with^{83 85-87 91 151}
 - (a) Iodine often ineffective
 - (b) Propylthiouracil^{1 71}
- (2) Dosage—oral
 - (a) Lugol's solution—10 to 30 minims daily
 - (b) Propylthiouracil—200 to 300 mg daily
- (3) Management (see Chart 24)
 - (a) Propylthiouracil (or another antithyroid drug) is given

until basal metabolic rate becomes normal

- [1] Dosage may be reduced or maintained

- [2] A longer time is required for response than ordinary hyperthyroid patient

- [3] Lugol's solution (if not taken previously) for 10 days preoperatively

- [4] Myxedema may be produced with possible enlargement of thyroid gland¹

- (b) Subtotal thyroidectomy is performed if

- [1] Goiter is present
- [2] Patient is in good condition

- (c) Roentgen therapy over pituitary continued as needed

- (d) Basal metabolic rate may remain elevated without¹

- [1] Signs of hyperthyroidism

- [2] Palpable goiter

- [3] Effect from antithyroid drugs¹⁰³

- [4] Increased uptake of radioactive iodine¹⁰¹

2 Diabetes

a Management (see 85 \VI)⁷⁰

- (1) Customary regime as for all diabetic patients
- (2) Disease may be controlled to great extent by treatment of primary disorder as discussed with
 - (a) Roentgen therapy
 - (b) Surgery
 - (c) Estrogens^{1 1}

b Complications

- (1) As in other diabetics
- (2) Increase in insulin resistance suggests greater pituitary activity

3 Headache

a Temporary relief with

- (1) Roentgen radiation
- (2) Surgery
- (3) Analgesics
- (4) Sedatives

Vision impaired Further therapy not recommended, operation advised

- 55 Hair on chest and around pubic area has fallen out Shaves less Breasts still show enlargement RBC 6,200,000 Hgb 13.1 Gm Differential count not remarkable Plasma cholesterol 66 mg % Serum phosphorus 5.5 mg % Adrenal water test normal Operation—right frontal craniotomy with removal of pituitary adenoma Serum phosphorus 7 mg % and 5.5 mg %, in first postoperative week.
- 58 Patient died at home 3 months later, from meningitis (postmortem examination)

Comment Hyperpituitarism beginning after onset of puberty resulting in partial gigantism and acromegaly Severe apocrine gland infection Patient responded to roentgen therapy for visual disturbance Estrogens caused atrophy of testes, breast development and may have increased the size of pituitary tumor Progressive enlargement of sella in spite of roentgen therapy necessitated an operation, which was performed successfully Death occurred 3 months later from an acute meningitis Pathologic diagnosis pituitary tumor compatible with the diagnosis of eosinophilic adenoma Eosinophilia was not demonstrated because specimen was unfortunately fixed in Zenker's solution with acetic acid

TABLE 7 ACROMEGALY

Measurements of sella over 4 year period by anteroposterior depth and lateral contour areas in square millimeters

MONTHS	RIGHT AREA IN SQ MM	LEFT AREA IN SQ MM	MEAN AREA IN SQ MM	RIGHT AP	RIGHT DEPTH	LEFT AP	LEFT DEPTH	ROENTGEN THERAPY IN R UNITS	ESTROGEN (mg./24 hrs)
On admission	290	486	388	23	15	23	22		
21	320	620	470	23	15	33	22		
34	258	793	520	24	15	35	27	1 800	
36								1 800	
38	258	793	520	25	22	35	30	1 800	
40									Estrone 3 75
42	474	836	680	30	15	43	27		Estrone 3 75 Stilbestrol 6
45	325	590	407	26	20	38	25		Stilbestrol 6
49	598	810	707	33	21	37	25	1 800	Stilbestrol 6
50									Stopped
52	506	939	7 2	30	20	42	27		
53	Operation								

REFERENCES

- Albright, F. Reifstein E. C. Jr and Forbes A. P. Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 12th Meeting Feb. 4-5 New York Josiah Macy Jr. Foundation 1946 pp. 97-104
- Albright, F. and Reifstein E. C. Jr. Parathyroid Glands and Metabolic Bone Disease p. 196 Baltimore Williams & Wilkins Co. 1948
- Almy, T. P. and Shorr, E. Disappearance of diabetes mellitus associated with acromegaly following acute mastoiditis and basilar meningitis Assoc. Study Int. Secretions 1947 p. 19
- Althausen, T. L., Lockhart, J. C. and Soley, M. H. New diagnostic test (galactose) for thyroid disease Am. J. Med. Sc. 199 342-351 (Mar.) 1940
- Astwood, E. H. Thiouracil treatment in hyperthyroidism J. Clin. Endocrinol. 4 229-248 (June) 1944
- Atkinson, F. R. B. Acromegaly description of papers reported in 1935, 1936, 1937 Endocrinologic 20 245-257 (July) 1938
- Acromegaly London Bale 1932
- Aub, J. C., Bauer, W., Heath, C. and Ropes, M.

XVII PROGNOSIS

A GENERAL

- 1 It depends on
 - a Rapidity of development
 - b Nature of tumor
 - c Response to treatment
 - d Associated diseases
- 2 Spontaneous cessation of growth hormone activity is common

B DURATION OF VARIOUS TYPES¹⁰ 11

- 1 Benign—may be 50 years
- 2 Chronic—from 8 to 30 years
- 3 Malignant (acute)—from 3 to 4 years

XVIII CAUSES OF DEATH¹¹

A FROM TUMOR

1 Extension

2 Hemorrhage

B CARDIAC COMPLICATIONS

- 1 Congestive heart failure
- 2 Auricular fibrillation
- 3 Coronary disease
- 4 Subacute bacterial endocarditis (rare)

C INTERCURRENT INFECTION (any kind)¹¹

- 1 Pneumonia
- 2 Influenza
- 3 Bronchitis

D DIABETIC COMA

E NEPHRITIS

F LEUKEMIA

G OTHER DISEASES

ACROMEGALY

PROTOCOL IX

FIGS 88 91, 94

CHART 23

Family history Negative

Past medical Negative

Chief complaint Enlarged hands and feet

History of present illness Patient was rejected by the draft board because of acromegaly of which he was unaware Shortly after puberty he started to grow rapidly until 19 years of age when he reached 78 in Furuncles for 3 years under arms and on the buttocks Shaves regularly Sex function normal No further increase in general size for 18 months No headache or visual change

Physical examination Age 21 male single Weight 235 lbs Height 78 in Span 79½ in Pulse 96 BP 150/90 Increase in size of acral parts Hair normal distribution Thyroid and genitalia normal Reflexes normal

Laboratory data Urine normal Glucose tolerance test (blood sugar mg %) fasting 100 ½ hr, 167 1 hr 134 2 hrs 78

Roentgenographic findings Skull—sella enlarged clinoids displaced backward, decalcification of anterior clinoids enlargement mainly on left side Epiphyseal status (bone age)—closed

Progress

MONTHS

- 12 No complaints Visual fields—slight defect in bitemporal fields Visual acuity—little change
- 20 Shoes the same No tremor or sweating Erections somewhat less Weight 240 lbs Height same BP 130/80 Pulse 96

Roentgenographic findings—see Table 7

- 32 Rarely headache Loss of sight in right eye suddenly, 2 months previously Roentgen therapy 1 800 r

- 33 No ejaculations possible Questionable hypoglycemic attack on one occasion

- 35 Roentgen therapy 1,800 r

- 37 Apocrine gland infection around perineum Glucose tolerance test (blood sugar mg %) ½ hr 97 1 hr, 175, 2 hrs, 189 3 hrs 165 Roentgen therapy 1,800 r

- 39 Serum protein 6.7 Gm % Plasma cholesterol 54 mg % Serum phosphorus 5.1, 4.7 4.9 and 3.9 mg %* 17 ketosteroids 6.5 mg/24 hrs Estrone 3 to 75 mg/24 hrs for 2 months Stilbestrol 6 mg/24 hrs for another 7 months

- 42 Sella turcica larger Roentgen therapy 1,800 r

- 51 Breasts enlarged and sore Apocrine gland infection better No headache Shaves every day Erections absent Weight 248 lbs BP 120/80 Hair decreased on body and chest Breasts pigmented Testicles smaller Penis pigmented Glucose insulin tolerance test no change Roentgen therapy 1 800 r

- 53 Head feels full Very constipated

* We are grateful to Dr Ann P Forbes for these reports

- 50 Fraer R W Forbes A P Albright F Solkowitz H and Reifenstein E C Colorimetric assay of 17 ketosteroids in urine: survey of use of this test in endocrine investigation diagnosis and therapy, *J Clin Endocrinol* 1 234 256 (Mar) 1941
- 51 Friedgood H H Similarity of iodine remission in experimental anterior hypophyseal hyperthyroidism hyperthyroidism of acromegaly and that of exophthalmic goiter *Endocrinology* 20 526 536 (July) 1936
- 52 Friedgood H H and Dawson A H Physiological significance and morphology of carmine cell in cat's anterior pituitary *Endocrinology* 26 1022 1031 (June) 1940
- 53 Fulton M N and Cushing H Specific dynamic action of protein in patients with pituitary disease *Arch Int Med* 50 649 667 (Nov.) 1932
- 54 Geddes A C Report upon the examination of the body of an acromegalic subject Edinburgh *M J* n.s. 2 218 234 1909
- 55 Goldberg M H and Lissner H Acromegaly: consideration of its course and treatment: report of 4 cases with autopsies pituitary adenoma *J Clin Endocrinol* 2 477 501 (Aug) 1942
- 56 — Hypogonadism in acromegaly, report of 2 cases with improvement from male and female sex hormone *Clinics* 1 644 654 (Oct) 1942
- 57 Henderson W R Sexual dysfunction in adenomas of the pituitary body *Endocrinology* 15 111 127 (Mar Apr) 1931
- 58 Hetzel K S Glycosuria in acromegaly *Lancet* 1 440 441 (Feb) 1926
- 59 Hin dale G Acromegaly *Medicine* Detroit Warren 1898, pp 43-44
- 60 *Ibid* p 30
- 61 *Ibid* p 23
- 62 *Ibid* pp 15 16
- 63 *Ibid* pp 20 and 27
- 64 — Acromegaly Syringomyelia Crossed Knee Jerks Anterior Poliomyelitis p 43 Philadelphia International Medical Magazine Co 1900
- 65 Hirsch O Surgery's contribution to our knowledge of pituitary function *Confinnia neurol* 7 45 54 1946
- 66 Horrax G Pituitary Gland pp 665 682 Baltimore Williams & Wilkins 1938
- 67 Howard J E and Bigham R S Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 8th Meeting Oct 13 14 New York Josiah Macy Jr Foundation 1944 pp 26 36
- 68 *Ibid* 10th Meeting New York N Y, June 15 16 New York Josiah Macy Jr Foundation 1945 pp 272-307
- 69 Hurxthal L M Unpublished data
- 70 Hurxthal L M and Dee J F Acromegaly *Lahay Clin Bull* 3 196 205 (Jan) 1944
- 71 Hurxthal L M Horrax G Hare H F and Poppen J L The treatment of acromegaly *J Clin Endocrinol* 1 126 148 (Feb) 1949
- 72 Hutchinson W M The pituitary gland as a factor in acromegaly and gigantism New York *M J* 72 89 100 133 145 (July) 1900
- 73 Hutton E L and Reiss M Hormone treatment of acromegaly *J Ment Sc* 88 550 553 (Oct) 1942
- 74 Jackson I Acromegaly partial removal of acidophil adenoma of pituitary followed by 2 pregnancies *Proc Roy Soc Med* 36 (May) 1943
- 75 John H J Spontaneous disappearance of diabetes *JAMA* 85 1629 1631 (Nov) 1915
- 76 — The possible relationship between acromegaly and diabetes with a report of three cases *Arch Int Med* 37 439 511 (Mar) 1926
- 77 Jones H M Possible anatomic relations between the pituitary body and the prostate gland *J Urol* 42 50 56 (July) 1939
- 78 Joslin E F Root H F White P Marble A and Bailey C C Treatment of Diabetes Mellitus ed 8 p 717 Philadelphia Lea & Febiger 1946
- 79 Junck E C Maddock W O and Heller C G Gonadotropic hormone: comparison of ultrafiltration and alcohol precipitation methods of recovery from urine *J Clin Endocrinol* 7 1 10 (Jan) 1947
- 80 Keith A An inquiry into the nature of the skeletal changes in acromegaly *Lancet* 1 993 1002 (Apr) 1911
- 81 Kim ell L W Michaels G D Li C H and Larsen W E Studies in growth I Interrelationships between pituitary growth factor and growth promoting androgens in acromegaly and gigantism II Quantitative evaluation of bone and soft tissue growth in acromegaly and gigantism *J Clin Endocrinol* 8 1013 1036 (Dec) 1948
- 82 Kirklin O L and Wilder R M Follicular hormone administered in acromegaly *Proc. Staff Meet Mayo Clin* 11 121 125 (Feb) 1936
- 83 Knäufel H F Jr Albright F and Griswold H C Experience with quantitative test for normal or decreased amounts of follicle stimulating hormone in urine in endocrinological diagnosis *J Clin Endocrinol* 3 529 544 (Oct) 1943
- 84 Kloppner K Die Störungen der weiblichen Sexualfunktion bei Erkrankungen des Vorderlappens Zweischchenhirnsystems *Arch f Gynak* 169 254 296 1939
- 85 Kolmer J A Clinical Diagnosis by Laboratory Diagnosis p 896 New York Appleton 1943
- 86 Krumbhaar E H Pituitary disorders in their relation to acromegaly (hyper pituitarism) with suggestions for the use of a more precise terminology *M Clin North America* 5 927 956 (Nov) 1921
- 87 Lammli K A Akromegaler Diabetes und Strumektomie *Deutsche med Wchnschr* 63 1568 (Oct) 1937
- 88 Lewis D D Hyperplasia of the chromophile cells of the hypophysis associated with acromegaly with report of a case *Bull Johns Hopkins Hosp* 16 157 164 (May) 1905
- 89 Lewis L A and McCullagh E P Plasma protein pattern (Tlelus electrophoretic technique) in Cushing's syndrome *J Clin Endocrinol* 7 559 565 (Aug) 1947
- 90 Li C H and Evans H M Biochemistry of Pituitary Growth Hormone Recent Progress in Hormone Research vol 7 pp 3 44 New York Academic Press 1949
- 91 Lomer E L Winkler A W Taylor F H L and Peters J P Intravenous glucose tolerance test *J Clin Investigation* 20 507 515 (Sept) 1941
- 92 Mahler P and Pasterny K Action of insulin in diabetes mellitus *Med Klinik* 20 337 340 (Mar) 1924

- Studies of calcium and phosphorus metabolism effects of thyroid hormone and thyroid disease *J Clin Investigation* 7 97 137 (Apr) 1929
- 9 Bailey P and Cushing H Studies in acromegaly: microscopical structure of adenomas in acromegalic dyspituitarism (fugitive acromegaly) *Am J Path* 4 545 564 (Nov) 1928
 - 10 Bailey P, and Davidoff L M Concerning the microscopic structure of the hypophysis cerebri in acromegaly (based on a study of tissues removed at operation from 35 patients) *Am J Path* 1 185 207 (Mar) 1925
 - 11 Barnett H L, Perley A M and Heinbecker P Influence of eosinophile cells of hypophysis on kidney function *Proc Soc Exper Biol. & Med* 32 114 116 (Feb) 1943
 - 12 Bartels E C Personal communication
 - 13 Bassoe F Endocrine growth disturbance—acromegaly gigantism dwarfism *M Clin North America* 5 85 (July) 1921
 - 14 Bauer W., and Aub J C Studies of calcium and phosphorus metabolism influence of pituitary gland *J Clin Investigation* 20 295 301 (May) 1941
 - 15 Bell H Quoted by R Moebig and G S Bates Influence of the pituitary gland on erythrocyte formation *Arch Int Med* 51 207 235 (Feb) 1933
 - 16 Bergum O Stewart F T and Hawk P B A study of the metabolism of calcium magnesium sulphur phosphorus and nitrogen in acromegaly *J Exp Med* 20 218 224 (Sept) 1914
 - 17 Blum L and Schwab H Diabète acromégalaque et Insuline *Compt rend Soc biol* 89 193 196 (June) 1923
 - 18 Borchardt L Die Hypophysenglykosemie und ihre Beziehung zum Diabetes bei der Akromegalie *Ztschr f Klin Med* 66 332 343 1908
 - 19 Brook Harlow Acromegaly pp 72 *Ill Utica N Y, State Hospitals Press* 1899
 - 20 Chasoff J, Friedfeld L and Tunick A M Hyperparathyroidism in patient with acromegaly *Ann Int Med* 16 162 175 (Jan) 1942
 - 21 Chester W and Chester E M Vertebral column in acromegaly *Am J Roentgenol* 44 551 557 (Oct) 1940
 - 22 Coggeshall C and Root H F Acromegaly and diabetes mellitus *Endocrinology* 26 1 25 (Jan) 1940
 - 23 Colwell A R The relation of the hypophysis to diabetes mellitus *Medicine* 11 1-40 (Feb) 1927
 - 24 Courville C H and Mason V R Heart in acromegaly *Arch Int Med* 61 04 713 (May) 1935
 - 25 Creutzfeldt H G Ein Beitrag zur normalen und pathologischen Anatomie der Hypophysis cerebri des Menschen *Mit a d Hamb Staatskrankenanst* 9 273 294 1909
 - 26 Cummings J N Creatine metabolism in relation to pituitary tumours *Brain* 67 265 269 (Sept) 1944
 - 27 Cushing H Pituitary Body and Its Disorders Philadelphia Lippincott 1912 pp 30-44
 - 28 *Ibid* pp 132 170
 - 29 — "Dyspituitarism" 20 years later with special consideration of pituitary adenomas *Arch Int Med* 51 487 557 (Apr) 1933
 - 30 — The Weir Mitchell lecture Surgical experiences with pituitary disorders *J.A.M.A* 63 1515 1525 (Oct.) 1914
 - 31 Cushing H and Davidoff L M The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance No 22 New York Monograph Rockefeller Institute for Medical Research 1927
 - 32 Davidoff L M Studies in acromegaly anamnesis and symptomatology in 100 cases *Endocrinology* 10 461-483 (Sept-Oct) 1926
 - 33 Davidoff L M and Cushing H Studies in acromegaly disturbances of carbohydrate metabolism *Arch Int Med* 39 751 779 (July) 1927
 - 34 Davis A C The thyroid gland in acromegaly a study of 166 cases *Tr Am A Study Gutter* 1940 pp 312-321
 - 35 Davis L Principles of Neurological Surgery 3rd Edition p 176 Philadelphia Lea & Febiger 1946
 - 36 Davis A C Thyroid gland in acromegaly *Proc Staff Meet Mayo Clin* 9 709 714 (Nov) 1934
 - 37 — Thyroid gland in acromegaly study of 166 cases *J Clin Endocrinol* 1 445-449 (May) 1941
 - 38 Dott V M and Bailey P A consideration of the hypophyseal adenomata *Brit J Surg* 13 314 366 (Oct) 1925 26
 - 39 Dyle C G and Hare C C Pituitary Gland pp 651 664 Baltimore Williams & Wilkins 1938
 - 40 Edsall D L and Miller C W A contribution to the chemical pathology of acromegaly *Univ Penn M Bull* 16 1903 1904 1943
 - 41 Erdheim J Ueber einen Hypophysentumor von ungewöhnlichem Sitz *Beitr z path Anat u z Allg Path* 46 333 240 1909
 - 42 — Über Wirbelsäulenveränderungen bei Akromegalie *Virchows Arch f path Anat* 281 231 296 (June) 1911
 - 43 — Die pathologisch-anatomischen Grundlagen der Hypophysären Skelettveränderungen (Zwergwuchs Typus Frühlich Akromegalie Riesenwuchs) *Fortschr a d Geb d Röntgenstrahlen* 52 234 245 (Sept) 1935
 - 44 Escanilla R F Diagnostic significance of urinary hormonal assays report of experience with measurements of 17 ketosteroids and follicle stimulating hormone in the urine *Ann Int Med* 30 249 290 (Feb) 1949
 - 45 Falta W Ductless Glandular Diseases p 246 Philadelphia Blakiston 1915
 - 46 Fellinger K Klinische und experimentelle Untersuchungen über das Verhalten und die Bedeutung des thyreotropen Hormons im Blute *Wien Arch f inn Med* 29 375-406 1936
 - 47 Flatau G and Rall H A case of acromegaly studied during the course of the disease and at autopsy *Endocrinology* 26 229 235 (Feb) 1940
 - 48 Franchini G Sul ricambio materiale in un caso di acromegalia (Über den Stoffwechsel in einem Falle von Akromegalie) *Biochem Centralbl Ref* 3 522 1904 1905
 - 49 Fraser R W Albright F and Smith H Value of glucose tolerance test, insulin tolerance test and gluco c insulin tolerance test in diagnosis of endocrinologic disorders of glucose metabolism *J Clin. Endocrinol.* 1 297 306 (Apr) 1941

- 135 Squires R H and Thannhauser E J Acromegaly with secondary multiple endocrine insufficiency, case report with study of nitrogen metabolism and its connection with glycosuria Bull New England M Center 3 335-341 (Dec) 1941
- 136 Starr P and Davis L Endocrine studies of patients after subtotal hypophysectomy Ann Surg 113 778 790 (Mar) 1941
- 137 Ibid Illinois Med J 78 486 492 (Dec) 1940
- 138 Stephens D J Suppression of lactation in acromegaly during estrogenic therapy Endocrinology 25 638 641 (Oct) 1939
- 139 Sternberg M Beitrage zur kenntniss der Akromegalie Ztschr f klin Med 27 85 150 1894
- 140 Tauszk F and Vas H Beitrage zum Stoffwechsel bei Akromegalie Pest med chir Presse 35 193 201 1899
- 141 Teel H M The effect of the growth principle of the hypophysis on the female genital tract with the report of the hypertrophic changes in a case of acromegaly Endocrinology 13 521 528 (Nov Dec) 1929
- 142 Tompsett S L and Oastler E G The determination of the total 17 ketosteroids in urine a simplification of the method for routine use in a hospital biochemical laboratory Glasgow M J 27 281 297 (Oct) 1946
- 143 Ulrich H Insulin in acromegaly diabetes, Arch Int Med 43 785 795 (June) 1929
- 144 — The antagonism between insulin and pituitary extract Arch Int. Med 41 875 881 (June) 1928
- 145 Vaughan W W Place of irradiation in acromegaly report of 53 cases Am. J Roentgenol 40 660 668 (Nov) 1938
- 146 Venning E H and Brown J S L Excretion of glycogenic corticoids and of 17 ketosteroids in various endocrine and other disorders J Clin Endocrinol 7 79 101 (Feb) 1947
- 147 Wayne H Bennett, G A and Bauer W Joint disease associated with acromegaly Am. J M Sc. 209 671 687 (May) 1945
- 148 Weidler W B Acromegaly with extreme degree of exophthalmos Boston M & S J 174 506 (Apr) 1916
- 149 Weinstein A Response of acromegaly to deep roentgen ray therapy case report Ann. Int. Med 13 715 721 (Oct) 1939
- 150 Wolf W Endocrinology in Modern Practice, pp 57 58 Philadelphia Saunders 1939
- 151 Yater U M Acromegaly and diabetes Arch Int Med 41 883 912 (June) 1928
- 152 Zondek H The Diseases of the Endocrine Glands ed 4 p 322, Baltimore Williams & Wilkins 1944

- 91 Maranon P and Morros J Pituitary hyperglycemia and its possible value in diagnosis *Endocrinology* 13 564 572 (Nov Dec) 1929
- 92 Margitay Becht E Die Prolan Ausscheidung bei Akromegalie *Endokrinologie* 15 153 158 1935
- 93 Margitay Becht E and Miklós L Hormonuntersuchungen bei akromegalie *Klin Wchn chr* 10 2306 2308 (Dec) 1931
- 94 Marie F Sur deux cas d'acromégalie hypertrophie singulière non congénitale des extrémités supérieures inférieures et céphalique *Rev de méd* 6 297 333 1836
- 95 Mark Leonard Acromegaly A personal experience pp 1 158 London Baillière Tindall & Cox 1912
- 96 Marrian G F and Butler G C The hormones *Am Rev Biochem* 6 303 334 1937
- 97 Mason V R Heart in acromegaly *Tr A Am Physicians* 51 220 229 1936
- 98 McCullagh E P Tice Practice of Medicine in vol 8 p 404 Maryland W F Prior Co 1941
- 99 McCullagh E P Gold A and McHenry J B R Radioactive iodine uptake in hypermetabolism of acromegaly *J Clin Endocrinol* 10 687 692 (July) 1950
- 100 McCullagh E P and Hewlett J S Acromegaly as associated with amyotrophic lateral sclerosis and acromegaly of the amyotrophic type *J Clin Endocrinol* 7 636 643 (Sept) 1947
- 101 McCullagh E P Hibbs R E and Schneider R W Propylthiouracil in treatment of hyperthyroidism *Am J M Sc* 214 545 552 (Nov) 1947
- 102 McCullagh E P and Luga H V Bioassays for urinary androgens comparison of results in normal men with those having endocrine disturbances *Endocrinology* 25 753 764 (May) 1940
- 103 Medigreanu F and Kruteller L General metabolism with special reference to mineral metabolism in a patient with acromegaly complicated with glycosuria *J Biol Chem* 9 109 120 1911
- 104 Moehlig R C Acromegaly—Case report with autopsy findings *Endocrinology* 25 134 142 (July) 1939
- 105 Moehlig R and Bates G S Influence of the pituitary gland on erythrocyte formation *Arch Int Med* 51 207 235 (Feb) 1933
- 106 Monnier M and Steinmann J Hormontherapie Schweiz med Wchn chr 74 155 159 (Feb) 1944
- 107 von Morawski W D Stoffwechsel bei Akromegalie unter der Behandlung mit Sauerstoff Phosphor etc *Ztschr f klin Med* 43 336 360 1901
- 108 Morgan J Anaemia in Rhesus negative woman during pregnancy with Rhesus positive foetus *Proc Roy Soc Med* 38 326 (May) 1945
- 109 Nutescu I I and Timus D Die Ausscheidung des thyreotropen Hormons aus dem Hypophysenvorderlappen durch den Harn bei Akromegalie *Spital* 58 31 1938
- 110 Oberndorfer H Ueber den Stoffwechsel bei Akromegalie *Ztschr f klin Med* 65 6 13 1908
- 111 Osborne H T A case of acromegaly autopsy skeleton *Tr A Am Physicians* 51 262 277 1897
- 112 Perkin H J and Lahey F H Level of iodine in blood *Arch Int Med* 65 882 895 (May) 1940
- 113 Pfahler G E and Spackman E W Roentgen therapy in pituitary tumors *Am J Ophth* 14 796 807 (Aug) 1931
- 114 Putnam T J and Davidoff I M Pituitary Gland pp 714 724 Baltimore Williams & Wilkins 1938
- 115 Ravaut P Acromegalie avec diabète sucré tumeur du corps pituitaire et gigantisme viscéral *Bull et mem Soc méd d hop de Paris* 17 352-360 (Mar) 1900
- 116 Reifstein E C Jr Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing Symposium on Urinary Corticosteroids 10th Meeting June 15 16 New York Josiah Macy Jr Foundation 1945 pp 131 220
- 117 Reifstein E C Jr Kinsell L W and Albright F Observations on the use of the serum phosphorus level as an index of pituitary growth hormone activity the effect of estrogen therapy in acromegaly *J Clin Endocrinol* 4 0 (June) 1946
- 118 Reinhardt A and Creutzfeldt H H Beitrag zur Lehre von der Akromegalie *Beitr z path Anat u z Allg Path* 56 465 499 1913
- 119 Rocca F F and Perez D Accion de la folliculina sobre la diabetes acromegálica *Arch urug de med cir y especial* 26 1 14 (Jan) 1945
- 120 Roth O Auftreten von Milchsekretion bei einem an Akromegalie leidenden Patienten *Klin Wchnchr* 13 305 307 (Apr) 1918
- 121 Seale E A Pituitary tumor—gigantism *South African M J* 9 295 298 (May) 1935
- 122 Schiff A Hypophysis und thyreoidea in ihrer Einwirkung auf den menschlichen Stoffwechsel *Klin Wchnchr* 10 277 285 (Mar) 1897
- 123 Schittenhelm A and Buhler F Die Spontanleukämie bei innersekretorischen Störungen ihr Vorkommen und ihr diagnostischer Wert *Ztschr f d ges exper Med* 95 181 196 1935
- 124 Schurr I and Sharpey Schafer E F The inhibition of pituitary activity in acromegaly by oestradiol benzoate and testosterone propionate *Clin Sc* 3 413-418 (Dec) 1937
- 125 Schurr I Acromegaly and creatine creatinine metabolism *Quart J Med* 6 17 33 (Jan) 1937
- 126 — Creatine creatinine metabolism in adult and juvenile hyperpituitarism *J Endocrinol* 5 274 281 (June) 1948
- 127 Schultze F and Fischer H Zur Lehre von der Akromegalie und Osteoarthropathie hypertrophante *Mitt d Grenzgeb d med u Chir* 24 607 632 1911 12
- 128 Scriver W de M and Bryan A H Observations upon the calcium and phosphorus metabolism in a case of acromegaly showing marked osteoporosis *J Clin Investigation* 14 212 219 (Mar) 1935
- 129 Sendrail M and Tamalet L J Le test hypophysaire d'Aron en clinique Toulouse med 40 1 15 (Jan) 1939
- 130 Sosman M C Personal communication
- 131 Spark C and Baller S H Acromegaly with long standing tumor infiltration of cavernous sinuses *Arch Path* 35 93 111 (Jan) 1943
- 132 Speert H Ovarian granulosa cell tumor and acromegaly *J Clin Endocrinol* 9 610 635 (July) 1949



FIG 81 ACROMEGALY WITHOUT PROGNATHISM Age 32 Duration 2 years beginning after pregnancy Persistent lactation Headache No visual field defects Roentgen ray therapy (36 x 300 r) without effect on lactation or headache Temporary suppression of lactation with stilbestrol Increased size of sella Amenorrhea ceased after roentgen ray therapy



FIG 82 PROGNATHISM AND GOITER IN ACROMEGALY Age 34 Onset age from 14 to 15 gradual acral enlargement ceasing around age 30 Patient also had a nodular goiter and severe hyperthyroidism Complaints weight loss 50 lbs excessive perspiration palpitation weakness and severe back ache 3 years duration Bitemporal visual field defect enlarged sella de pressed into sphenoid sinus Weight 145½ lbs Pulse 168 BMR plus 81% After 7 days on Lugol's solution weight 148 lbs Pulse 88 BMR plus 37% Subtotal thyroidectomy in 2 stages Weight 1 year later 189 lbs pulse 80 no hyperthyroidism Orthopedic examination flexion deformity left hip with no rotation Pronounced kyphosis low dorsal region Pain Degenerative changes shown on roentgenograms of spine and hip joint

FIG 78 (Right) ACROMEGALY Probably the first published picture of acromegaly from Marie's original article (Marie P Sur deux cas d'acromégalie hypertrophie singulière non congénitale des extrémités supérieures inférieures et céphaliques Rev de méd 8 297 333)



FIG 79 (Below) PROGNATHISM IN ACROMEGALY Age 41 Duration 11 years Sella enlarged and depressed into spheroid sinus Slight temporal field defect Cervicodorsal kyphosis Amenorrhea menopausal Urinary FSH 3 plus Hand of patient compared with that of normal female on the right Note great overgrowth of tissue



FIG 80 LEONINA FACIES Age 29 male Showing deep furrows from overgrowth of facial tissues (leonina facies) Little or no prognathism

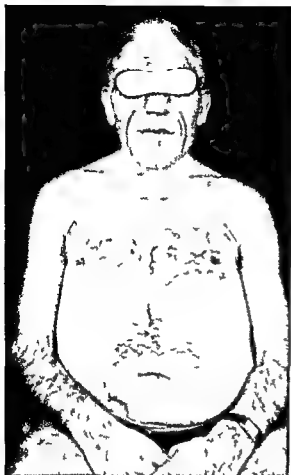


FIG 85 ACROMEGALY Age 56 Married at 22 Father of 3 children Acromegaly began at age of 40 although he noted no acromegalic changes until 50 years of age Patient never had body hair but after 40 it grew very rapidly He did not shave until 25 years old Patient has hypertension (BP 160/100) cardiac enlargement and coronary disease with transient nocturnal dyspnea and orthopnea EKG shows intraventricular block



FIG 86 ACROMEGALIC SKULL Age 36 male Duration 11 years Chief complaint supra orbital headache and transient blindness controlled by roentgenotherapy Leads normal life Father of 3 children since onset Note enlarged sella sinuses and prognathism



FIG 87 VERTEBRAE IN ACROMEGALY New growth (Erdheim J Die pathologische Anatomie der hypophysären Skelettveränderungen [Zwergwuchs Typus Frohlich Akromegalie Riesenwuchs] Fortschritte der Röntgenstrahlen 52 234)



FIG 83 ACROMEGALY WITHOUT PROGNATHISM Age 31 Onset from 7 to 8 years of age Amenorrhea since 19 Features gradually changed over a period from 7 to 8 years Gradual enlargement of hands and feet during 4 years Blurred vision and headaches for 1 year Loss of smell from 3 to 4 months Excessive sweating Musculature and body configuration has masculine tendencies Spadelike hands Note large nose and molluscum fibrosum Skin coarse Tongue normal Normal complete blood count fasting sugar total protein A/G ratio glucose tolerance test and glucose insulin tolerance test Sellar size 24×26 mm Roentgenography



FIG 84 ACROMEGALY IN A YOUNG FEMALE Age 20 Duration around 2 years Chief complaints swelling of hands and enlargement of face Marked acne Catamenia normal Blood pressure 160/110 Visual fields normal Serum phosphorus 5 mg % Plasma cholesterol 176 mg % Glucose tolerance curve $\frac{1}{2}$ hr 96 mg % 2 hrs 204 mg % 3 hrs 163 mg % Note diabetic curve in disease of short duration Sella measured 15×18 mm area about 192 sq mm Progression in prognathism and sella size in spite of 16×300 r in 4 months of treatment Menorrhagia after first series of roentgen treatments Hypertension persisted and increased after therapy Rapid decrease in vision Operation and removal of adenoma followed by splanchuocectomy BP normal 1 year later serum phosphorus 3.4 mg %

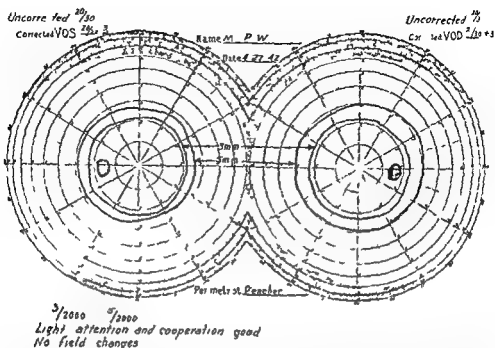


FIG 91 ACROMEGALY—VISUAL FIELDS (See Protocol 10 XIX Figs 88-94 Chart 23) Visual fields in progressive acromegaly and immediate effect of roentgenotherapy. This case illustrates importance of early treatment and regular observation (*Above*). On first examination (*Below*) One year later defects evident no visual disturbance noted by patient roentgenotherapy should have been given at this time (*Opposite page top*) Twenty two months later the patient first noted visual changes 2 months prior to this observation (*Opposite page bottom*) Six weeks after 6 roentgen ray treatments 300 r each further improvement did not take place in spite of 24 more treatments 300 r each during the ensuing year

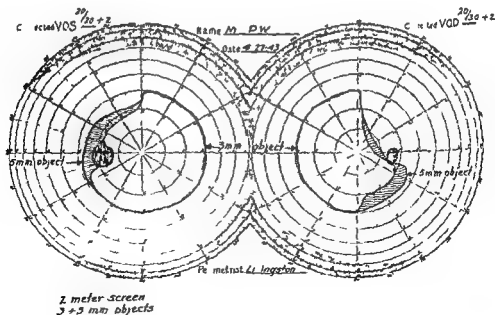




FIG 88 PROGRESSIVE ENLARGEMENT OF SINUSES IN ACROMEGALY (See Protocol 10 VII Figs 91-94 Chart 23) (Left) First observation (Right) Observation 3 years later. Note increase in size of frontal and maxillary sinuses.

FIG 89 (Right) ACROMEGALIC GIANT SKELETON. Note especially arm length indicating span greater than height and onset before epiphyseal closure (Bassoe P. Endocrine growth disturbance—acromegaly gigantism dwarfism. M Clin North Amer 10: 5-85).



FIG 90 (Bottom) ACROMEGALY. Age 51 female. Duration from 10 to 12 years. Marked osteo-arthritic changes especially involving hip joints and preventing external rotation of legs.





FIG 92 (Left) CONGENITAL PROGNATHISM
WITHOUT ACROMEGALY



FIG 93 (Right) FUGITIVE ACROMEGALY Age 30 Although this patient had all the signs of a chromophobe tumor it should be noted that fairly large hands and feet prognathism and prominent frontal bossae are present Such findings would hardly be expected in view of a bone age of 16 if the entire process had been initiated by this type of tumor There fore it is probable that some hyperpituitarism existed for a few years and was followed by hypopituitarism His chief complaints were attacks of mental confusion depression agitation and loss of both libido and beard growth Repeated transient visual acuity changes were unrelieved by roentgenotherapy RBC 3.9 million Hgb 68% Plasma cholesterol 304 mg % BMR minus 32% Craniotomy by Dr J L Poppen Satisfactory response to oral testosterone therapy

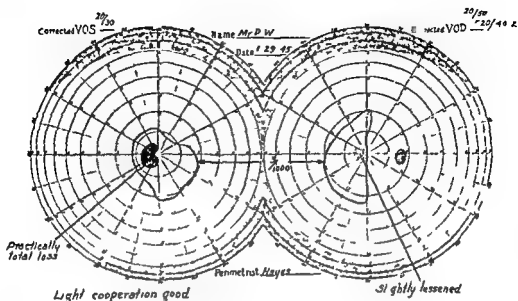
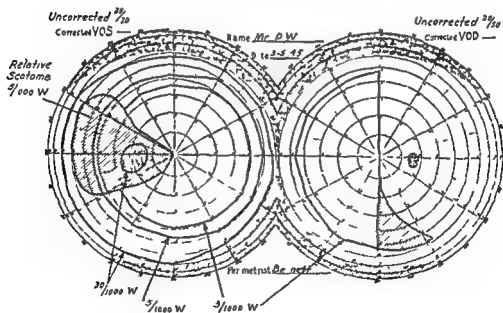


FIG 91 ACROMEGALY—VISUAL FIELDS Continued



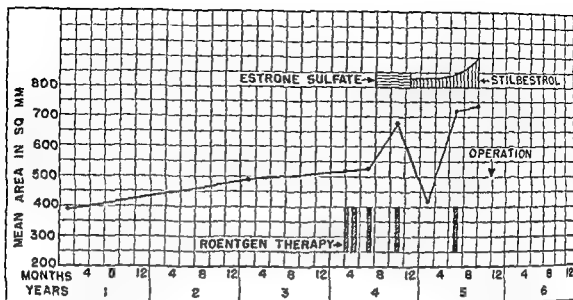


CHART 23 ACROMEGALY (See Protocol 10 \N Figs 88 91 94) Mean lateral contours of sella in square millimeters showing increasing size during observation during which time roentgen and estrogen therapy were given Possible deleterious effect of large doses of estrogens is suggested

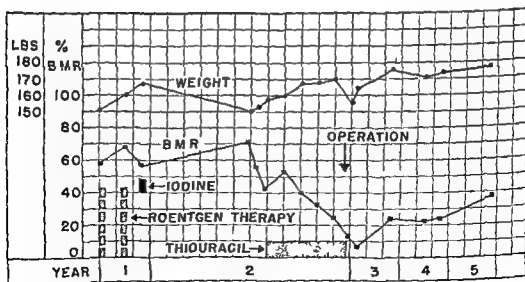


CHART 24 ACROMEGALY Chart of BMR and weight in acromegaly showing effect of the ouracil (0.6 Gm daily) Two courses of roentgenotherapy (2400 r each) had no effect Lagol's solution (30 mums a day) caused no clinical improvement Subtotal thyroidectomy was performed at end of second year Note gradual rise of BMR during 3 years after operation at which time the total blood iodine was 30.4 micrograms %

CHART 22 ACROMEGALY Glucose tolerance curve in an acromegalic female (A) Before treatment weight 131 lbs pulse 72 BMR plus 4% (B) One year after treatment of pituitary tumor weight 151 lbs pulse 56 BMR minus 4%. Patient age 48 who had acromegaly probably 10 years or more was treated first with roentgenotherapy with temporary improvement in vision. Later an operation was performed because of sudden and rapid visual failure. Complete restoration of vision followed with no recurrence.

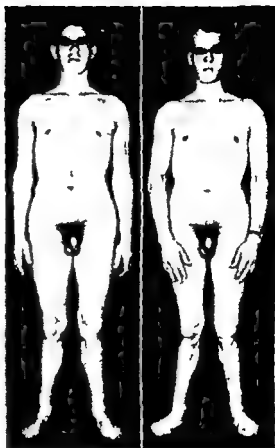
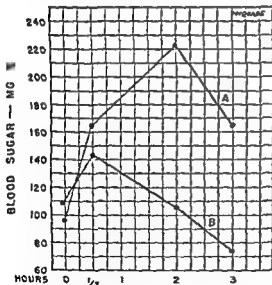


FIG 94 ACROMEGALY (See Protocol 10 VII Figs 83-91 Chart 23) (Left) Age 20 Onset shortly after puberty. Patient as he appeared on the first examination. (Right) Patient immediately at the time of operation 4 years later. Note loss of hair on abdomen and body as well as decreased amount surrounding pubic area. There has been considerable atrophy of testes slight increase in size of breasts as well as darkening of the areolae. This probably resulted from estrogen therapy. There appears to be a change in stance. Note also prominence of clavicles.

b Temperature	Normal, but cold extremities with acrocyanosis at times
■ Moisture	Not remarkable
d Eruptions	Acne, ecchymoses, telangiectasis ³⁸
■ Pigmentation	May be some brownish discoloration small or large pinkish to deep purple (occasionally white) striae on abdomen, hips, axillae, arms, breasts (see Frontispiece) ³⁸
f Color	Plethoric, cyanosis of hands, feet, face, mottling
2 Hair	
a Head	Normal or brittle and dry, may show loss ^{114 116 151} hair line low on forehead ¹¹⁴
b Facial	Slight to marked increase in females, no definite alteration in males perhaps less than normal ¹¹⁴
■ Axillary	Normal, may be scanty ³⁷
d Pubic	Normal, masculine distribution in females with adrenal tumor may be scanty ³⁷
■ Body	Occasionally marked hirsutism, less frequent in males
F HEAD	
1 Shape and size	Normal but appears large and round
2 Facial expression	Moon face or pig eyed, dull, dreary
3 Eyes	
a General	Appear small because of facial fat exophthalmos some times but slight (probably hypertensive feature) ^{9 34 ■ 90 114 135 137 138 14 189 19*}
b Fundi	Normal optic edema if hypertensive with retinal hemorrhages and/or exudates ⁷⁸
c Visual	
(1) Fields	Normal could be reduced with pressure of large tumor ^{74 108}
(2) Acuity	Normal unless reduced by hypertensive changes
4 Ears and nose	Normal
5 Mouth and throat	
a General	Normal pig mouth
b Teeth	Normal or carious periodontal membrane may be lost
c Larynx (voice)	Variable
G NECK	
1 General	Excessive fat short rounded and joins trunk with heavy fat pads
2 Thyroid	Normal rarely palpable
H CHEST	Normal contour except for dorsal round back and/or kyphosis
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal or enlarged from hypertension
2 Rate and rhythm	Normal unless cardiac decompensation
3 Blood pressure	Rarely normal usually elevated with relatively high diastolic pressure
4 Peripheral arteries and veins	Normal or forceful pulsations with hypertension
5 Vasomotor	See <i>Integument E1</i>
J BREASTS	
1 Male	Normal
2 Female	Normal may show striae or galactorrhea ¹⁷⁷ if onset starts before puberty no development ¹³⁰

SECTION 11

CUSHING'S SYNDROME

(Pituitary Basophilism)

I DEFINITION

A condition which when fully developed is characterized by obesity of the trunk and the head, plethora, purplish striae of the skin hypertension and osteoporosis amenorrhea \equiv almost always found in females impotence and atrophic testes may be present in males, slight to moderate hirsutism in females \equiv often observed, polycythemia and glycosuria are frequently noted, the following outline pertains to Cushing's syndrome regardless of cause or age

II APPEARANCE

Buffalo type of obesity, moon face, hirsutism, plethora multiple pinkish to deep purple striae on protuberant abdomen upper arms and legs axillae and breasts when disease is fully developed (see Figs 95 98, 100 to 102)

III AGE

Any, third decade most frequent³⁰⁻³⁵

IV SEX

Females predominate

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal variation or dull

B RESPONSIVENESS

Related to degree of mental aberration^{20 151}

C OTHER ABNORMALITIES

Usually depressed confused, anxious lethargic, may be psychotic late in disease, and have suicidal intentions (see Protocol 11 XXI)^{70 75 130}

VI PHYSICAL STATUS

A NUTRITION

Normal or obese thin extremities which may show muscular atrophy, undernutrition causes loss of weight as in normal person⁶⁰

1 Weight

Increased, may lose later in illness

2 Fat distribution

Rapidly acquired around face neck trunk abdomen may be painful face rarely involved alone \equiv unusual fat distribution may be due to skeletal deformity,⁶⁰ but this does not explain moon face (see 106 III E 13)

B HEIGHT

Normal or slight decrease if kyphosis or dorsal round back \equiv present

C EXTREMITIES

Loss of flesh

1 Upper

Normal or appear thin and may show loss of weight

a Hands

Normal occasionally cyanotic

b Fingers

Normal occasionally cyanotic

c Span

Normal relationship unless marked kyphosis

2 Lower

Thin in comparison with rest of body acrocyanosis of legs

a Feet

Normal cyanosis and/or edema sometimes

b Toes

Normal occasionally cyanosis

D SPINE

Dorsal round back and/or kyphosis

E INTEGUMENT

1 General

Tight over obese areas nails brittle or hard

a Texture

Thin, little subcutaneous substance bruises easily parch ment texture¹

11 Reticulocytes	Normal ¹¹⁷
12 Prothrombin time	Normal or slightly prolonged ³⁹
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal or high (for references see D 1 a below)
2 Nonprotein nitrogen	Normal or increased ^{27 31 33 4 5 7 8 11 114 201}
a Urea nitrogen	As for nonprotein nitrogen ^{18 30 33 107 13 137 139 141 151 164 187 188 190}
3 Protein	Normal or slightly decreased ^{6 7 8 37 2 4 5 30 35 39 122 177 181 1 3 174 188}
a A/G ratio	Normal or increased ^{37 31 37 60 138}
4 Uric acid	Normal ^{31 37 60 137}
5 Cholesterol	Variable ^{18 37 39 41 45 53 54 55 1 23 30 33 38 107 138 117 121 177 137 140 141 143 161 171 188 193 201}
6 Sodium	Normal, increased or decreased rarely ^{3 4 5 53 65 114 11 1 1 7 153 173 190}
7 Potassium	Normal or decreased ^{4 8 9 60 114 141 1 7 188 190}
8 Calcium	Usually normal, may be decreased ^{17 18 30 31 37 39 43 45 53 58 59 77 80 90 95 114 117 177 132 13 143 147 164 174 181 187 188 193 199 200 201}
9 Phosphorus	Normal or decreased (see Protocols 11 XIII XIV) ^{30 53 55 9 77 78 90 95 99 10 117 1 7 140 145 147 184 178 185 187 188 191 199 200 201}
10 Chlorides	Normal or decreased ^{37 39 43 45 53 90 10 114 177 164 187 188 199}
11 Phosphatase	Normal or increased (see Therapy) ^{39 43 45 53 80 114 117 140 141 164 137 193 200}
12 Iodine	No data
13 Creatine	Increased ¹⁸³
14 Creatinine	Normal ^{31 37 193}
15 Magnesium	Variable ^{30 1 7 183 190}
16 Carbon dioxide combining power	Normal or increased ^{17 45 90 137 155 188 190}
17 Icterus index	May be increased
D FUNCTION TESTS	
1 Tolerance (see Chart 25)	
a Glucose	Normal, but more often diabetic curve ^{1 3 4 8 18 5 20 31 33 37 39 43 45 49 53 56 58 61 63 3 77 81 90 98 10 106 113 114 116 117 141 23 137 14 143 164 174 19 183 187 190 193 200 201 116 117 141 23 137 14 143 164 174 19 183 187 190 193 200 201}
b Glucose insulin	Decreased (hyperglycemic unresponsiveness) ^{3 6 7 174}
■ Insulin	Curve shows resistance ^{1 39 56 7 174}
d Galactose	Normal, low or rarely high curve ^{1 8}
2 Adrenal water	Positive or negative ¹¹³
3 Salt deprivation	Decreased capacity for excreting chlorides in high concentration ^{9 143 164 188} (DOCA does not cause sodium chloride retention, as in normals, ^{21 143} when the latter is given intravenously—see 2 XIII E 2 b)
4 Balance	
■ Nitrogen	Negative early in disease later may be slightly positive ^{1 4 37 38 43 99 140 147 156 196}
b Calcium	May be negative usually follows nitrogen balance ^{1 13 39 77 95 101 137 140 143 183}
c Phosphorus	Normal ^{15 38 98 102}
d Iodine	No data

K. ABDOMEN	Protuberant
1 Liver	Normal
2 Spleen	Normal
3 Hernia	None
4 Tumor	Adrenal or ovarian (see Differential Diagnosis)
L. GENITALIA	
1 Male	
a Penis	Normal or atrophied in adults retarded and small if onset occurs before puberty (see Protocol 11 \\\)
b Testes	Normal size and consistency or some atrophy
■ Prostate	Normal ⁷⁸
2 Female	
a External	Normal or slight enlargement of the clitoris which is most marked with an adrenal tumor ³³
b Internal	Normal may have enlarged cystic or atresic ovaries ³³
M. NEUROMUSCULAR	
1 Muscles	Often severe weakness
2 Gait	Normal, unless vertebrae affected by multiple fractures and collapse, or when associated with weakness standing or walking may be impossible
3 Body movements	Normal
4 Tremor	May occur ^{114 115}
5 Paresthesias	May be present
6 Reflexes	Normal
N. SPEECH	Normal

VII LABORATORY DATA

A. URINE	
1 General	Normal volume may be increased
2 Special analyses	
a Sugar	May be present often excessive
b Albumin	Occasionally present
c Nitrogen	Variable
d Creatine	Normal ¹² or increased ¹¹
e Creatinine	Low excretion, may be half of normal ^{1 3 11 33}
f Sodium	Decreased ^{9 159}
g Potassium	Increased ⁶
h Calcium	Normal or slight increase
i Phosphorus	Variable ^{15 102, 147}
j Iodine	No data
B. HEMATOLOGY	
1 Red blood cells	Normal or polycythemia ^{-1 38 78}
2 Hemoglobin	Normal or increased ^{33 78}
3 White blood cells	Normal or increased (about 10 000 to 12 000) ¹⁰
4 Differential	Normal absolute or relative polymorphonuclear leukocytosis marked and absolute lymphocytic leukopenia ¹⁰ total eosinophils below 150 cu mm ¹³⁷
5 Hematocrit	Increased ⁵
6 Platelet count	Normal ^{117 118}
7 Fragility	Normal ¹⁸⁸
8 Bleeding time	Normal ⁷⁸
9 Coagulation time	Normal ⁷⁸
10 Clot retraction	Normal ⁷⁸

H EPIPHYSEAL STATUS
(bone age)

Normal rarely delay in prepubescent union of epiphyses
37 45 58 179 1.0 187 201

C LONG BONES

Normal, except for decalcification and if marked may result in fractures, fragmentation of heads of femurs and metatarsals

D VERTEBRAE

Kyphosis, may have collapsed multiple fractures, ankylosis, fish spine, decalcification with thin biconcave bodies separated by large intravertebral disks (expanded nucleus pulposus⁵⁸), special predilection for vertebrae and pelvis⁷

E BONE TEXTURE

- 1 Osteoporosis
- 2 Fractures

Cranium, pelvis, spine
Spontaneous (see Fig 99)

F MISCELLANEOUS

- 1 Chest
- 2 Pelvis

Lower ribs are enlarged and some may be fractured¹⁷
callous formation seems adequate sternum may be protruberant from collapsed ribs, thymoma may be found¹⁰
May show decalcification

IX ETIOLOGY

A UNKNOWN—Question of excessive secretion by basophilic cells due to

- 1 Overstimulation (possibly through hypothalamus⁷²—see 88 VIII K)
- 2 Abnormal cell rests

B PITUITARY—Basophilic adenoma may or may not be found

C ADRENAL CORTEX⁷¹

- 1 Hyperfunction
- 2 Hyperplasia
- 3 Carcinoma
- 4 Adenoma (see Protocol 11 VII Fig 98)

D OTHER CAUSES (see Pathology)

- 1 Carcinoma
 - a Pituitary
 - b Thyroid (see Frontispiece)
- 2 Granulosa cell tumor
- 3 Arrhenoblastoma (?)
- 4 Thymic tumor
- 5 Hypothalamic nuclei atrophy
- 6 No gross pathology^{11 45 68}

X PATHOLOGY

A GROSS^{19 21 29 50 58 61 98 107 12 133 151 173}
187 189

- 1 Pituitary¹⁷⁸
 - a Normal^{11 45 68}
 - b Adenoma
 - (1) Chromophobe^{37 61}

- (2) Acidophilic⁷⁰
- (3) Basophilic^{30 38}
- (4) In pars intermedia^{118 119}
- c Sarcoma¹⁰⁴
- d Carcinoma (may metastasize)^{10 54}

2 Thyroid

- a Normal
- b Small
- c Enlarged
- d Adenoma
- e Colloid goiter with adenoma
- f Atrophy

3 Parathyroids

- a Normal
- b Atrophy³⁷
- c Enlarged
- d Adenoma^{37 38}

4 Adrenals

- a Normal
- b Cortical hyperplasia
- c Adenoma
- d Carcinoma
- e Fatty degeneration
- f Tumor with atrophy of peripheral normal gland tissue

5 Testicles

- a Normal
- b Small
- c Atrophy

6 Ovaries

- a Normal
- b Senile with cysts

5 Renal	
a Phenolsulfonphthalein	Normal or decreased
b Clearance	
(1) Urea	Normal or decreased ^{7,8}
(2) Creatinine	Normal ¹¹⁴
E MISCELLANEOUS	
1 Basal metabolic rate	Rarely above plus 20 per cent or below minus 20 per cent
2 Circulation time	Normal unless cardiac failure
3 Sedimentation rate	Variable, theoretically should be low ^{29 83 97 114 III 148}
4 Specific dynamic action of protein	Increased ^{27 101}
5 Gastric analysis	Normal or achlorhydria ^{45 92}
6 Electrocardiogram	Normal or myocardial damage ^{3 39 54 67 77 98 116 133}
7 Blood volume	Not increased ¹
8 pH	Increased ¹⁰⁰
9 Total base	Decreased ^{19 77}
10 Spinal fluid	Irritant substance negative ^{1 7 148 190}
11 Fecal excretion	
a Calcium	High ^{24 59}
b Phosphorus	High ⁹
F URINARY HORMONE ASSAYS	
1 Follicle stimulating hormone	Variable, usually less than normal ^{7 31 3 34 50 51 61 65 69 86 97 98 114 137 142 16 201 201}
2 Luteinizing hormone	No data
3 Estrogens	Variable generally lower than normal ^{7 34 4 64 66 III 101 114 115 137 153 III 191 19}
4 Pregnanediol	May be present with amenorrhea ¹⁴³
5 17 ketosteroids	Normal or slightly elevated rarely markedly elevated ^{1 3 4 7 23 2 30 3 43 43 48 51 67 68 68 114 150 151 140 143 148 153 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000}
6 11 oxysteroids (glycogenic units)	Upper normal to greatly increased (also in blood) ^{4 9-8 22 41 4 143 175 17 186 197}
7 Aschheim Zondek	Negative ^{17 19 45 50 58 75 84 90 100 11 14 16} or positive ^{24 27 104}
8 Thyrotropic hormone	Negative or increased ^{7 33 140}
9 Corticotropin	Increased (also blood) ^{14 76 8 8 143}
G Biopsy	
1 Endometrial	Hypoplastic ¹¹⁴
2 Testicular	See 11 A B 2
H VAGINAL SMEAR	Low to moderate estrin effect even with amenorrhea ⁷⁸ neoplasticlike cells reported with normal catamenia ⁴
I SEMEN ANALYSIS	Normal or decreased count

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL	
1 Cranial vault	Normal later shows progressive decalcification (osteoporosis) may have mottling or ground glass appearance
2 Sella turcica	Normal rarely enlarged (see Protocol 11 X, IV) ^{78 108 114}
3 Mandible	Normal
4 Sinuses	Normal
5 Teeth	Normal

XI PATHOLOGIC PHYSIOLOGY

(see 39 VI B)

A INTRODUCTION

- 1 The chief disturbance is considered to be one of adrenocortical function (hyperfunction and/or dysfunction)
- 2 Observations and deductions to date may be summarized as follows for clinical purposes

B BUFFALO OBESITY

- 1 Its rapid acquisition early in the disorder suggests hypothalamic hyperphagia although this phenomena may be present in cases due to adrenal tumor
- 2 Clinical observations on use of ACTH and cortisone demonstrate relation to excess 11 oxysteroid hormones of adrenal cortex^{88 89}

C PURPLISH STRIAE THINNING OF SKIN AND WASTING OF MUSCLES

- 1 Reifstein (quoted by Albright⁴) attributes these findings to failure of tissue synthesis due to antianabolic effect of "S" hormones a theory which has been questioned¹
- 2 Demonstrable carbohydrate changes in some cases of full blown Cushing's syndrome are not always present
- 3 Negative nitrogen balance (excess excretion of urinary nitrogen over amount taken in food) is seldom demonstrated but tissue wasting and osteoporosis are considered as evidence that this has occurred¹⁴⁶
- 4 Excess of urinary 17 ketosteroids reflect the "N" hormone metabolism ACTH increases 17 ketosteroid excretion suggesting relationship however cortisone, an "S" hormone causes hair growth
- 5 While administration of testosterone may result in a greater positive nitrogen balance the same action occurs in conditions where N hormone is not lacking
- 6 The results of testosterone therapy may be attributed to offsetting the anti-anabolic effects of 'S' hormones as well as increasing the ratio of N S thus creating a positive nitrogen balance
- 7 A defect in protein splitting or in conversion of fat or glucose into the proper

amino acids for tissue synthesis may be another cause of muscular wasting osteoporosis and other findings this effect, too, is essentially antianabolic

- 8 In 1 case studied by Wilkins, the following was observed¹⁰⁸

- a A negative nitrogen balance resulted with an intake of 97 Gm of nitrogen, equilibrium was then established on 15 Gm (cortin excretion an indication of 'S' hormones, was reduced on this low nitrogen intake)
- b When 97 Gm of nitrogen were given again, a positive balance occurred lasting for 30 or more days
- c This phenomena suggests that when the body was not overloaded with protein, its ability to produce amino acids for tissue synthesis was restored, possibly due to a decrease in the secretion of "S" hormones
- d In rats given adrenocorticotrophic hormone on the other hand, Ingle found the least loss of nitrogen was on a high protein diet and greatest on a high fat intake⁸⁰

D VASCULAR HYPERTENSION

1 Adrenocortical hormones

- a There may be a direct effect on renal function by the hormones as shown by a decrease in⁸
 - (1) Blood flow
 - (2) Glomerular filtration
 - (3) Tubular secretion
- b A relationship to the electrolytic changes which are occasionally found is possible^{3 8 10 127 138 190}
 - (1) Urinary loss of
 - (a) Potassium
 - (b) Chloride
 - (2) Blood
 - (a) Potassium—decreased
 - (b) Sodium—increased
 - (c) Carbon dioxide combining power—increased due to chloride loss^{90 127 138 190}

- 2 Desoxycorticosterone (DOCA) given to animals and men in sufficient amounts causes¹⁹⁰

- a Hypertension
- b Sodium retention
- c Chloride retention
- d Potassium loss

- 3 Vascular changes in Cushing's syn

- c Fibrosis
- d Atrophy
- e Enlarged and contain corpora lutea
- f Granulosa-cell tumor
- g Sclerotic
- h 'Adrenal like' tumor²³
- i Arrhenoblastoma (?)¹³¹
- 7 Pancreas
 - a Normal
 - b Atrophy with arteriosclerosis of islets of Langerhans
 - c Enlarged
 - d Fatty degeneration
- 8 Pineal
 - a Normal
 - b Enlarged
- 9 Thymus
 - a Involted usually²⁹ ¹⁰⁶
 - b Carcinoma²⁰ ¹⁰⁶
 - c Enlarged¹⁶ ¹⁷³
 - d Replaced by fat³⁸ ¹⁸⁹
- 10 Kidneys
 - a Normal
 - b Malignant nephrosclerosis
 - c Nephritis¹⁷⁰
 - d Stones
- 11 Liver
 - a Normal
 - b Nutmeg³⁰
 - c Focal fatty degeneration⁷³
- 12 Spleen
 - a Normal¹⁸⁰
 - b Atrophy⁴¹
 - c Hyperplasia⁷
- 13 Lymph nodes are atrophic
- 14 Bones
 - a Normal
 - b Osteoporosis
 - (1) Very soft¹³¹
 - (2) Crack easily
 - c Fibrous osteitis
 - d Osteomalacia (?)²⁵
 - e Hyperostosis³
- 15 Atherosclerosis (generalized)³⁹

B Microscopic

- 1 Pituitary
 - a Various types of adenomas have been found
 - b Basophilic adenoma is the most common¹⁷⁹
 - (1) Size
 - (a) Macroscopic
 - (b) Microscopic

- (2) It may be present in
 - (a) Normal individual
 - (b) Other conditions¹²⁹
- (3) Basophilic cells show Crooke's changes³⁷ which are characteristic for Cushing's syndrome but are not diagnostic²⁹ ⁴⁸ ⁴⁹ ⁸¹ ⁹³ ¹⁰⁰ ¹¹⁰ ¹⁷⁰ ¹⁷¹
 - (a) These changes may be secondary to those in the adrenal cortex, including tumor¹³ ¹⁴
 - (b) Significance of cellular changes is unknown⁶¹ ⁸¹ ¹⁷⁶ ¹²⁸ ¹⁴¹ ¹⁴⁵ ¹⁸⁵
- (4) Crooke's changes in basophilic cells show³⁷
 - (a) Hyalinization
 - (b) Vacuolization (peripheral)
- c Cancer of basophilic cells rarely demonstrated²¹
- d Amphophil cells (take acidophilic or basophilic stain) are found in¹¹⁸ ¹²⁸
 - (1) Cushing's syndrome
 - (2) Cases of virilism (cancer or hyperplasia of adrenal cortex)
- 2 Testes³⁷ = 61 = 131
 - a Seminiferous tubules
 - (1) Normal
 - (2) Atrophy (see Fig 97)
 - (3) Spermatozoa
 - (a) Normal or abnormal
 - (b) Numerous or few
 - b Interstitial tissue
 - (1) Normal
 - (2) Edematous
 - (3) Cells may be
 - (a) Normal
 - (b) Sparse
- 3 Hypothalamic nuclei may show atrophy⁷³

TABLE 8 AUTOPSY FINDINGS IN CASES COLLECTED BY THOMPSON AND EISENHARDT¹⁷⁸

ASSOCIATION WITH TUMOR	Number of Cases		
	TOTAL	EXAMINED	CROOKE'S CHANGES
Pituitary adenoma	60	39	35
Adrenal tumor	22	11	11
Thymic tumor	3	3	3
Arrhenoblastoma	1	1	1
No tumor of any gland	12	9	8
Total	98	63	58

XII SYMPTOMATOLOGY

A NEUROMUSCULAR AND SENSORY

- 1 Headache
- Asthenia
- 3 Fatigability
- 4 Backache
- 5 Pain in extremities
- 6 Insomnia
- 7 Vertigo
- 8 Convulsions⁹¹
- 9 Unconsciousness
- 10 Mental depression
- 11 Eyes
 - a Dimness of vision
 - b Diplopia (transient)
 - c Pain around orbits

B CARDIOVASCULAR

- 1 Palpitation
- 2 Dyspnea
- 3 Angina

C GASTRO INTESTINAL

- 1 Polyphagia^{55, 10}
 - a Early—common complaint
 - b Later—decreased
- 2 Polydipsia^{5, 10}
- 3 Excessive weight gain
 - a Peculiar distribution
 - b Painful sometimes
- 4 Anorexia (due to uremia)

D GENITO URINARY

- 1 Amenorrhea (rare exceptions⁴)
- 2 Oligomenorrhea⁷⁸
- 3 Impotence
- 4 Polyuria
- 5 Nocturia

E GENERAL—Hypertrichosis

XIII DIAGNOSIS

A HISTORY

- 1 Mental changes
- 2 Stature shrinks
- 3 Obesity
 - a Rapid accumulation
 - b Characteristic distribution at
 - (1) Face
 - (2) Trunk
- 4 Appetite
 - a Early in disorder—voracious
 - b Later—decreased
- 5 Libido lost
- 6 Amenorrhea in most cases regular catamenia is rare⁴

7 Fractures

8 Renal colic

B PHYSICAL EXAMINATION—Check for

- 1 Obesity—buffalo type
- 2 Plethora
- 3 Purplish striae
 - a Upper arms
 - b Axillae
 - c Abdomen
 - d Buttocks
 - e Thighs
 - f Absent
- 4 Hypertrichosis
- 5 Ocular fundi for retinal changes
- 6 Hypertension is usually present
- 7 Dorsal round back
- 8 Adrenal tumor
- 9 Testicular hypoplasia
- 10 Pelvic tumor, under anesthetic if necessary

C LABORATORY

- 1 Complete blood count
- 2 Blood chemical analyses
 - a Nonprotein nitrogen
 - b Cholesterol
 - c Phosphorus
- 3 Tolerance tests
 - a Glucose
 - b Glucose insulin
 - c Insulin
- 4 Basal metabolic rate

D ROENTGENOLOGIC STUDIES

- 1 Skull
 - a Sellar size (see 2 \IV H)
 - b Teeth
 - Osteoporosis
- 2 Spine
- 3 Chest
- 4 Abdomen
 - a Kidney stones
 - b Adrenal tumor
- 5 Pelvis
- 6 Air inflation (kidney area)

E DIAGNOSIS

- 1 The advanced case is easily recognized but early ones may present difficulties
- 2 If significant hypertension or amenorrhea is absent any 4 of the following 7 items should establish the diagnosis
 - a Obesity (characteristic type)
 - b Loss of libido
 - c Amenorrhea
 - d Purplish striae

drome are not exactly analogous to those produced by an excess of deoxy corticosterone (DOCA), although it is tempting to explain the hypertension as due to it or a similar steroid

- 4 A large intake of protein or salt may play a role in the production of hypertension when adrenal cortical hormones are increased

5 Pressor substances

- a Little is known about these in this disorder
- b Renin may be increased by the amorphous fraction of the adrenals

E CARBOHYDRATE METABOLISM

- 1 Diabetes in Cushing's syndrome is attributed to an excess of carbohydrate or 'S' hormones i.e., 11 oxysteroids, of the adrenal cortex
- 2 Varying degrees of insulin resistance are caused by these hormones through the retardation of glucose oxidation or utilization^{61 72 81 11 181 190}
- 3 Conversion of proteins to sugar is increased for energy purposes which may contribute to
 - a Hyperglycemia
 - b Glycosuria
- 4 Burning of fat is accelerated to save the proteins

F SUSCEPTIBILITY TO INFECTION

- 1 Protection against toxins infections or other forms of stress is lowered
- 2 Excess of S hormones natural or synthetic (Compounds A E and F) cause dissolution of¹⁰
 - a Lymphoid tissue (i.e. lymphocytes)
 - b Thymus
 - c Lymph nodes
- 3 The effects or results¹⁰⁴
 - a Immune or protective globulins are released
 - b Circulating lymphocytes decreased
 - c Polymorphonuclear cells are increased
 - d Protection against toxins in the experimental animal
 - e In Cushing's syndrome these reservoirs are depleted rendering the patient more susceptible to noxious agents¹
 - f As Ingle points out this is a catabolic function not merely antianabolic⁸⁰

G HYPERTRICHOSIS

- 1 Is present in majority of cases
- 2 May be attributed to increased adrenal steroids (11 oxysteroids or 17 keto steroids) in an individual with hypertrichotic anlage

H GONADS

- 1 Both males and females (with rare exceptions) have a decreased function
- 2 Urinary gonadotropins are not decreased or increased, which is phenomenal considering the extent of change
- 3 Masculinization i.e., lowering of voice enlargement of clitoris is rarely present in the female cases
 - a If present one must postulate an increase in
 - (1) 'M' hormone
 - (2) Androgenic steroids
 - b Urinary 17 ketosteroids do not necessarily reflect the androgenicity of original adrenal steroids for they may be only metabolic end products

I OSTEOPOROSIS

- 1 Antianabolic effect of the excess (11 oxysteroids) hormones is probably responsible for
 - a Failure of laying down of bone matrix²
 - b Nonutilization of
 - (1) Calcium
 - (2) Phosphorus
- 2 Although negative calcium balance has rarely been proved,¹ its existence is probable in earlier stages of the disease (nitrogen phosphorus and sulfur may also be affected)¹⁰⁰
- 3 Impairment of calcium and phosphorus absorption by gastro intestinal tract has been demonstrated³
 - a Calcium is retained when given intravenously^{10 140}
 - b Osteomalacia may also be present in this disorder
 - c Some believe that vitamin D facilitates calcium absorption^{50 140} (in this disease the problem is controversial)
 - d Testosterone is effective, whereas estrogens are not in creating positive calcium balance

J DISTURBANCE IN PSYCHE—No logical explanation can be offered for this

- (3) Absence of adrenal pathology especially adrenal carcinoma

b Procedure—see 13 IX

c Results (see Protocol 11 XXIV)

- (1) From first series
 (a) Probably none
 (b) Backache may be relieved
 (c) Menses may return
 (d) Acne may subside
- (2) Subsequent series—final results variable¹ 3 15 16 30 37 43 47
 60 74 7 9 00 09 10 114 116 131
 137 14 144 16 167 174 178 00 201
- (3) Rotational therapy appears to be superior⁷⁸

2 Adrenal tumor or glands^{131 167}

a Indications

- (1) Nonresectable tumor
 (2) Failure of other therapy

b Procedure and dosage depend on

- (1) Tumor
 (a) Size
 (b) Location
 (2) Patient's condition

■ Results—not known

C IMPLANTATIONS OF RADON SEEDS IN PITUITARY^{3 1 0 139}

1 Indications

- a If extensive surgery is contraindicated
 b If roentgen therapy has been unsuccessful

2 Procedure

- a Transphenoidal route
 b Dosage—1 millicurie/cc of normal tissue

3 Dangers

- a Infection
 b Blind placement (radon seeds may not be inserted within tumor)

4 Result—some good reports³⁷

D SURGICAL

1 Adrenals

■ Indications

- (1) Unilateral
 (a) Removal of tumor^{0 1 90}
 9 96 114 19
 (b) First step in 2 stage operation for bilateral resection
- (2) Bilateral subtotal resection of normally appearing or hypertrophied tissue with⁹

- (a) Uncontrolled disease
 (b) Bilateral hypertrophy

(3) Denervation—not known⁸¹

b Comments

- (1) An adrenal gland should not be removed until the presence of the other gland has been demonstrated^{78 168}

- (2) Surgery is less hazardous

c Results—bilateral subtotal resection has not been proved yet as a sound therapeutic procedure in spite of several reported cures, recurrence possible without pituitary irradiation (see Protocol 11 XXIII)⁹

2 Pituitary

a Indications

- (1) Adrenals
 (a) Negative exploration
 (b) Unsuccessful partial resection
- (2) Roentgen therapy failed to achieve results
- (3) Sella is enlarged
- (4) Generally not advisable^{8 108}

b Results

- (1) Success rare
 (2) Mortality high (see Protocol 11 XX)

E MISCELLANEOUS

1 Testosterone^{1 43 140 187 193}

a Indications

- (1) Late stages of disorder for
 (a) Weakness
 (b) Weight loss
- (2) With roentgen therapy
 (a) For additional beneficial effects
 (b) If a failure
- (3) Preoperatively for same purpose as (1)
- (4) Postoperatively for
 (a) Adrenal tumor cases
 (b) Hastening recovery

b Dosage

- (1) Methyltestosterone—oral or buccal 30 to 50 mg daily
- (2) Testosterone propionate—intramuscular, average 25 mg daily to 3 times a week

c Results of both medications

- (1) Increase in^{140 193}

- e Hypertension
- f Osteoporosis
- g Diabetes
- 3 Exploration of the adrenals in most cases, even though no tumor can be demonstrated, may be required
- 4 Sometimes the tumor may be located in
 - a Sella turcica
 - b Chest
 - c Pelvis

- b Striae may be
 - (1) Small
 - (2) Pink color
- c Hypertrichosis
- d Hypertension
- 2 The following are normal
 - a Hematology
 - b Blood chemical analyses
 - c Urinary hormone assays
 - d Bone texture

XIV DIFFERENTIAL DIAGNOSIS

A ADRENOGENITAL SYNDROME (see 42 VIII)

- 1 Females
 - a Precocious development in children
 - b Masculinization in adults
 - c Amenorrhea common but exceptions have been reported
- 2 Males
 - a Condition is rare
 - b Spermatogenesis possible^{107 108}
- 3 Height age—increased
- 4 Fat distribution—normal
- 5 Striae—absent
- 6 Clitoris—usually prominent
- 7 Musculature—well developed⁷⁴
- 8 Blood chemical analyses—normal¹¹¹
- 9 Bone
 - a Age—advanced
 - b Texture—normal

10 Adrenal tumor—may be found

B ARRHIENOBLASTOMA (see 73)

- 1 Body contours—masculine
- 2 Fat distribution—normal
- 3 Absence of
 - a Striae
 - b Ecchymosis
 - c Acne (rare exceptions)
- 4 Blood pressure—normal
- 5 Sexual development—precocious in young
- 6 Clitoris—always enlarged
- 7 Ovaries
 - a Normal—often
 - b Tumor—may be palpable
- 8 Blood chemical analyses—normal
- 9 Bone
 - a Age—advanced in young
 - b Texture—normal

C FAMILIAL BODY CONTOUR ('Cushingoid' in pattern, but without Cushing's disease)

- 1 Members of family may have
 - a Similar build

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A INFECTIONS—Marked susceptibility to any type
- B DIABETES MELLITUS
- C ORTHOPEDIC PROBLEMS—Fractures
 - 1 Spontaneous
 - 2 Compression
- D CARDIOVASCULAR
 - 1 Hypertensive changes
 - 2 Renal damage
- E PSYCHOSES
 - 1 Depressive state
 - 2 Confusion
 - 3 Suicidal tendency

XVI TREATMENT

A INTRODUCTION

- 1 No definite course of therapy can be advised which will ensure success
- 2 Listed below are the various treatments used for this most unusual disease
- 3 In general roentgen therapy over the pituitary should be tried especially if an enlarged sella is found
- 4 If, on the other hand, the condition is serious and with evidence of rapid progression the adrenal glands should be explored for
 - a Adenoma
 - b Carcinoma
- 5 Bilateral subtotal resection or total removal of one adrenal and subtotal excision of the other may be indicated
- 6 Spontaneous recovery is possible in mild cases

B ROENTGEN^{70 120 167}

- 1 Pituitary
 - a Indications
 - (1) Sella turcica enlargement
 - (2) Trial before exploration and/or adrenal resection

- [3] Nitrogen balance
- [4] Phosphorus balance
- (b) Menstrual response unpredictable (see Protocol 11 XXIII)⁷⁸
- 3 Electrolyte balance
 - a Calcium
 - (1) Dosage
 - (a) Oral
 - [1] Lactate—10 to 30 Gm daily
 - [2] Chloride—10 to 30 Gm daily
 - (b) Intravenous—gluconate, 10 to 20 cc of 10 per cent solution
 - (2) Results
 - (a) Retention with intravenous administration^{39 140}
 - (b) Debatable if absorbed from^{1 15 9 140}
 - [1] Diet
 - [2] Oral medication
 - b Vitamin D
 - (1) Dosage—oral, 50 000 or more units daily
 - (2) Results—questionable retention of
 - (a) Calcium
 - (b) Phosphorus
 - c Potassium
 - (1) Acetate or chloride
 - (a) Dosage—oral 10 Gm daily
 - (b) Results^{8 11 17 189}
 - [1] Potassium level increased
 - [2] Hypochloremia corrected
 - [3] Alkalosis converted to normal
 - [4] Electrocardiogram may revert to normal
 - (2) Citrate
 - (a) Dosage—oral 10 Gm daily
 - (b) Results
 - [1] Potassium level increased
 - [2] Electrocardiogram changes may revert to normal⁵
- G SUMMARY OF RESULTS (from adrenal surgery, prolonged roentgen therapy and/or testosterone) (see Figs 100 and 101)^{33 7}
 - 1st 167
 - 1 Unfavorable—disease may progress to fatal outcome
 - 2 Favorable (if part or all the following take place)
 - a Increase in
 - (1) Strength
 - (2) Weight
 - b Color in striae may fade
 - c Ecchymotic tendency is lost
 - d Hypertrichosis decreases
 - e Blood pressure lowered
 - f Catamenia re established
 - g Libido may return (possibly)
 - h Bone changes
 - (1) Pain relieved
 - (2) Recalcification
 - (a) Healing of fractures
 - (b) Laying down of bone around compressed vertebrae
 - (c) Nucleus pulposus recompressed
 - i Hematology^{9*}
 - (1) Decrease in
 - (a) Red blood cells
 - (b) Leukocytosis
 - (2) Increase in
 - (a) Lymphocytes⁹
 - (b) Eosinophils⁷⁸
 - j Blood chemical analyses
 - (1) Decreased
 - (a) Sugar (see Chart 25)
 - (b) Nonprotein nitrogen
 - (2) Increased
 - (a) Calcium
 - (b) Phosphorus
 - (c) Phosphatase
 - k Balances—retention of
 - (1) Nitrogen
 - (2) Calcium
 - (3) Phosphorus

XVII PROGNOSIS

A INTRODUCTION—The following is based upon impressions as no large series of cases has been reported

B WITHOUT TREATMENT

- 1 Rapid fatal course, especially with
 - a Severe hypertension
 - b Coronary disease
 - c Malignancy
- 2 Spontaneous recovery is possible^{1 10}

- (a) Weight
 - (b) Strength
 - (c) 17 ketosteroids (may decrease with methyltestosterone¹⁴⁸)
 - (2) Improvement in
 - (a) Diabetes
 - (b) Skin changes
 - (3) Creatine
 - (a) Excretion—increased (can be prevented by testosterone propionate)
 - (b) Blood level—increased
 - (4) Creatinine excretion^{43 190}
 - (a) Normal
 - (b) Increased slightly
 - (5) Nitrogen balance may be increased, but less retention with continued usage^{1 3 43}
 - (6) Calcium
 - (a) Decrease in^{1 3}
 - [1] Excretion
 - [2] Retention
 - (b) Balance (recalcification of bones)
 - [1] No change^{140 190}
 - [2] Increased^{1 3}
 - (7) Phosphorus
 - (a) Balance—increased^{1 3}
 - (b) Retention—less marked with prolonged use¹¹⁰
 - (8) Phosphatase (serum)—rise delayed (an index of bone matrix formation)^{1 3 43 133}
- 2 Insulin
- a Indications (see 85 XVI D 1)
 - (1) Diabetes
 - (2) Glycosuria which is uncontrollable with diet
 - b Dosage
 - (1) Dependent on severity of condition
 - (2) Regulate as in any diabetic
 - (3) May require comparatively higher doses than in ordinary diabetes
 - c Results—fairly good control
- 3 Diet
- a Low protein gradually increase amount^{115 196}
 - b Limited sodium intake may be helpful⁹
- 4 Antihypertensive therapy
- a Hypertension may persist after the various treatments, probably due to renal damage⁷⁴
 - b Low sodium diet, ammonium chloride or thiocyanates may be effective
 - c Splanchnectomy might be temporarily helpful
- F OBSERVED EFFECTS OF OTHER ATTEMPTED THERAPY
- 1 Comment—the real value of the following ■ dubious potassium salts are the chief items which have shown corrective tendencies although producing little clinical change
- 2 Hormones
- a Estrogens^{3 16 43 44 47 53 179 184 193 249 1.2. 195 198}
 - (1) Dosage
 - (a) Variable
 - (b) Oral or intramuscular methods tried^{43 47 113}
 - (2) Results
 - (a) Urinary excretion⁴³
 - [1] Creatine—slightly increased
 - [2] Creatinine—decreased
 - (b) No alteration in balance of³
 - [1] Nitrogen (prolonged usage produces retention)
 - [2] Calcium
 - [3] Phosphorus
 - (c) Variable clinical improvement has been reported
 - [1] Subjective usually
 - [2] Little effect on
 - [a] Weight loss
 - [b] Plethora
 - [c] Hypertrichosis
 - [d] Blood pressure
 - [e] Genitalia
 - [f] Amenorrhea
 - (d) It has been given with testosterone without synergistic action^{1 2}
- 3 Progesterone
- (1) Dosage—intramuscular 10 to 25 mg daily
 - (2) Results^{1 3 44}
 - (a) Little effect on
 - [1] Cholesterol (plasma)
 - [2] Sugar curve

phorus 10.1 mg % Serum chlorides 99.5 mEq/l Serum carbon dioxide 72.2 vol % Serum total fatty acids 14.7 mEq/l Glucose tolerance test normal curve (may have been altered due to thyroidectomy) PSP 47% excretion in 30 min BMR minus 40% EKG normal Urinary hormone assays male sex hormone, 3 IU daily (normal adult male 25 IU), female sex hormone, 50 IU daily (normal adult male 25 IU)

Röntgenographic findings (At New Haven Hospital) Generalized decalcification, deformity of vertebral bodies of lower dorsal spine pathologic fractures of ribs, ischia and left pubis with callous formation Cardiac enlargement and widening of supra cardiac shadow Urograms were indeterminate

Treatment and progress Irradiation of pituitary, 5 series each consisting of 4 treatments on successive days Exploration of left adrenal—normal Patient was referred to the Lahey Clinic for exploration of the pituitary gland Physical examination the same except testicular atrophy was noted Operation by Dr Gilbert Horrax—no pituitary tissue removed Postoperatively the patient seemed to do very well for the first 4 days but then developed signs of intra-

cranial pressure and pneumococcal meningitis which caused his death

Postmortem findings Anatomic diagnoses purulent meningitis, healed fractures adposity, cutaneous striae, aortic fibrous peritoneal adhesions, testicular atrophy, pulmonary atelectasis, recent craniotomy with partial resection of right frontal lobe healed upper left quadrant incision Microscopic pituitary—high degree of hyalinization as described by Crooke, large cyst of the pars intermedia lined with ciliated epithelium, no basophilic adenoma Testes—tubules shrunken with increased basement membrane slight spermatogenic activity and very few mitoses present, interstitial tissue was edematous with rather rare shrunken (interstitial?) cells Adrenals—normal, no cytochemical studies made however

Summary Classical Cushing's syndrome associated with Crooke's changes in the pituitary The onset of the disorder was interesting and suggests the possibility of failure of the adaptation syndrome, with the patient remaining in the stage of counter shock and/or stage of resistance The hazards of surgery and susceptibility to infection is well illustrated Antibiotic therapy was not available then

CUSHING'S SYNDROME

Family history Negative

Past medical Patient was rejected by Army because of nervousness

Chief complaints Nervousness, exhaustion and variation in weight for 13 months

History of present illness Patient had been in good health until 13 months ago when he gained 40 lbs in 1 month due to an increased appetite and craving for sweets He became emotionally upset, exhausted, sleepy and lost about 26 lbs on a diet Because of a low BMR his physician gave him thyroid tablets (dosage not known) without improvement or effect on his weight During the next 6 to 8 months he developed mental sluggishness and depression, intolerance to cold, decreased libido and more marked fatigue Severe headache for 3 months, worse with sneezing cough

PROTOCOL XXI FIG 98

ing or in recumbent position Also low back pain and aches in his arms and legs

Physical examination Age 25 male, single Weight 147 lbs (usual weight 134, maximum 173) Height 70½ in BP 120/86 Florid, moon face and buffalo type of obesity (fat face neck and trunk with very thin extremities) Skin dry and coarse Deep purplish striae at axillae buttocks groins and thighs Eyelids puffy Marked dorsal round back Decrease in muscle mass of legs Slight weakness of his arms Hands mottled

Laboratory data Urine trace of sugar and albumin concentration 1.026 RBC 4,800-000 Hgb 15.6% WBC 11,400 Differential polymorphonuclears 75%, band forms 4% lymphocytes 11%, monocytes 10%, NPN 41 mg % Plasma protein 9 Gm %

C WITH TREATMENT

- 1 Surgery on
 - a Pituitary
 - (1) Hazardous
 - (2) Ill advised
 - b Adrenal
 - (1) Reasonably favorable with availability of cortisone
 - (2) Cancer decreases chances for recovery
- 2 Roentgen therapy over pituitary—if response favorable, outlook is fair, especially if hypertension is not progressive¹⁰⁷
- 3 Other forms of management are usually palliative

XVIII CAUSES OF DEATH⁸⁰

A INFECTIONS

- 1 Pneumonia⁷⁸
- 2 Septicemia
- 3 Tuberculosis
- 4 Meningitis⁷⁸
- 5 Erysipelas

B MISCELLANEOUS

- 1 Heart failure
- 2 Uremia
- 3 Apoplexy (see Protocol 11 \XII)⁷⁸
- 4 Pulmonary edema
- 5 Pancreatitis (acute)
- 6 Gastric ulcer
- 7 Metastases⁷⁸
- 8 Postoperative complications
- 9 Suicide

CUSHING'S SYNDROME

Family history Cardiovascular disease

Past medical Negative

Chief complaints Backaches, headaches, weakness and obesity of 3 years duration

History of present illness Patient was well until 5 years before admission. At that time he was confined in a State Penitentiary where because of a prison riot, he was put into solitary confinement for 90 days on bread stew and water diet. During this period he gained weight rapidly and developed a peculiar fullness of his cheeks and purplish striae on the lower part of his abdomen. The adipose tissue seemed to be concentrated at the upper trunk, head and neck. He became weak, nervous and irritable with increased sweating, headaches, dyspnea, polydipsia, frequency and complete loss of libido. His hair remained the same. Three years later while in prison a thyroidectomy was attempted but only a pole ligation was done. Eight months later a subtotal thyroidectomy was performed following which he became sluggish both mentally and physically. He was so weak that ordinary duties could not be performed. Six months later he grew progressively worse. Headaches were very severe, numbness of legs, rib and girdle pain at level of fifth to seventh thoracic vertebrae. One year later he was given 30 intramuscular injections of pituitary extract without

PROTOCOL \X FIGS 95-97

effect. By that time he had so many pains that following the roentgen findings of generalized decalcification he was put in a body cast for 20 days. Thereafter he was bedridden for 10 months and lost 30 lbs. He was admitted to New Haven Hospital as a patient of Dr. Harvey Cushing.

Physical examination (At New Haven Hospital) Age 25, male, single. Weight 130 lbs. Height 68 in. Pulse 100. BP 220/160. Extremely rubicund, thick buccal pads, obesity of trunk, neck and thin extremities. Marked kyphosis and tenderness over ribs and dorsal spine. Visual fields normal. Heart enlarged to left, distant sounds of fair quality. Abdomen obese, no masses or tenderness. Deep purplish striae over thorax, abdomen and hips. Few ecchymotic areas over lower extremities and many congenital pigmented moles on his face. Edema of feet and ankles.

Laboratory data (At New Haven Hospital) Urine normal. RBC 4,830,000. Hgb 95%. WBC 17,100. Differential: polymorphonuclears 87%, lymphocytes 10%, monocytes 2%, eosinophils 1%. Blood sugar 61 mg %. NPN 30 mg %. Serum total protein 5.67 Gm %. Serum albumin 4.00 Gm %. Serum globulin 1.67 Gm %. Plasma cholesterol 209 mg %. Serum sodium 131.4 mEq/l. Serum potassium 5.4 mEq/l. Serum calcium 9.58 mg %. Serum phosphorus 3.26 mg %. Serum lipid phosph

mEq/l Glucose tolerance test (blood sugar mg %) fasting, 81, $\frac{1}{2}$ hr, 196, 1 hr, 228, 2 hrs, 189 Glucose insulin tolerance test (blood sugar mg %) fast ing, 107, $\frac{1}{2}$ hr, 185, 1 hr, 189, 2 hrs, 192, 3 hrs, 125 4 hrs, 83 Urea clearance 56% PSP total 42% Urinary hormone assays estrin negative 17 ketosteroids 10.5 mg (volume 1,300 cc) and 17.8 mg / 24 hrs (volume 2,850 cc)

Roentgenographic findings Skull—sella normal, osteoporosis, teeth normal Multiple old fractures of ribs lungs clear, heart normal Urograms normal Abdomen normal, except for hypertrophic changes at iliac crests Osteoporosis of lumbosacral spine and pelvis Old fracture of ascending and descending rami of the pubis with dense calcification There is some calcification in the region of the trochanteric bursa on the left

Treatment and progress Pelvic examination and exploration of adrenals—"normal" Irradiation of pituitary area 5 series of 6 treatments, 400 r each, over a period of 18 months During this time patient injured her leg which ulcerated and healed very slowly First menstrual period occurred 3 months after first series of roentgen therapy Ten months after beginning of roentgen treatment there was no significant change in repeated blood counts Serum phosphorus increased Blood pressures aver

aged around 150/100 No change in 17 ketosteroids, alpha steroids were 7.3 mg and beta steroids 12.2 mg / 24 hrs At the end of a year, glucose tolerance test showed improvement (blood sugar in mg %) fast ing, 87, $\frac{1}{2}$ hr, 147, 1 hr, 135, 2 hrs, 107 No glycosuria Eighteen months after beginning of therapy, BP 180/120 Serum phosphorus 2.9 mg % Lymphocytes 19% Periods regular and patient feels in good health Weight 135 lbs One year later patient had cerebral apoplexy with hemiplegia

Summary This case illustrates the rather severe hypertension along with all other characteristic signs of Cushing's syndrome Adrenal exploration was negative Roentgen therapy caused resumption of normal catamenia and general improvement BP initially was 198/140 and 1 year later after several courses of roentgen therapy it was 150/102 Without further treatment, BP rose to 180/120 in 9 months Initially the serum phosphorus was 2.1 mg %, and at time of lowest blood pressure, 4.9 mg % During next 9 months, it was 2.9 and 3.1 mg % as BP rose again In view of failure to bring about permanent reduction in BP with irradiation, the question, in retrospect is whether bilateral resection of adrenals might not have accomplished this The answer is unknown, for this procedure is not always successful in this regard

CUSHING'S SYNDROME

PROTOCOL XXIII

FIGS 99 AND 100

CHART 137

Family history Father died of cardiovascular disease Brother died of hypertension, under age of 30

Chief complaint Weakness weight gain, hirsutism, fullness of face, headache irregular scant periods and finally amenorrhea

History of present illness Five years previous to admission, patient noted gradual onset of chief complaints Weight gain, 42 lbs For 6 weeks, nocturnal dyspnea Edema of ankles for 2 weeks Pain in low back and legs

Physical examination Age 26, female Weight 137 lbs Height 59 in Pulse 88 BP 190/130 Moon face, hirsute and ruddy com

plexion Numerous purplish striae Fundi not remarkable Gallop rhythm

Laboratory data Urine albumin 0, sugar 0, specific gravity 1.013 sedimentation—few WBC RBC 5,300,000 Hgb 16.5 Gm (average) WBC 8,950 Differential polymorphonuclears 73% lymphocytes 13% monocytes 9% Platelets 208,000 Capillary fragility normal NPN 48 mg % Serum uric acid 5.4 mg % Serum phosphorus 3.3 mg % Plasma cholesterol 228 mg % Serum calcium 10.7 mg % Serum alkaline phosphatase 3.6 BU Urea clearance 49% of normal Urinary hormone assays FSH—weak positive estrin—Grade I, 17 keto

Serum sodium 145.3 mEq/l Serum potassium 12.9 mg % Serum calcium 10.1 mg % Serum phosphorus 3.9 mg % Alkaline phosphatase 4.1 B U Carbon dioxide combining power (serum) 54 vol % Glucose tolerance test (blood sugar mg %) fasting, 63, 1 hr, 157 2 hrs 115, 3 hrs, 65 Repeated test fasting 76 1 hr, 189, 2 hrs 127 Glucose insulin tolerance test fasting 70 mg %, ½ hr, 111 mg %, 1 hr, 149 mg % 2 hrs, 174 mg % PSP (intravenous) 45% excretion in 30 min Sedimentation rate 2 mm/hr Urinary hormone assays FSH weak positive 17 ketosteroids 39.2 mg/24 hrs

Röntgenographic findings: Skull, chest and urograms normal Thoracic spine coarse trabeculation, calcium content compatible with hyperparathyroidism

Treatment: Preoperative therapy testosterone, 50 mg daily for 1 week Benzedrine, 5 to 10 mg b.i.d. Exploratory operation excision of adrenal cortical tumor, size of orange Postoperative course uneventful Desoxycorticosterone 10 to 20 mg and cortical hormone, 30 cc for several days in decreasing doses Intravenous 10% glucose—2,000 cc daily for 4 days with added

penicillin 200 000 units daily

Progress: Patient improved physically, but because of marked mental depression was transferred to the Psychopathic Hospital and then to Danvers State Hospital Four months later he died of bronchopneumonia

Postmortem findings: (Danvers State Hospital) Autopsy revealed no unusual changes other than bronchopneumonia and fibrinous pleuritis Microscopic findings pituitary—glandular portion consisted mostly of chromophobes and eosinophilic cells, the nervous portion showed columns of basophilic cells invading the glandular part, Crooke's changes not noted Thyroid—atrophic, fibrous tissue replaced most of glandular tissue

Summary: This case illustrates Cushing's syndrome due to adrenal cortical tumor, which was discovered only by exploration Serum sodium slightly increased, serum potassium low, and mild alkalosis yet no significant hypertension Essentially normal glucose tolerance but an equivocal glucose insulin tolerance curve Although bone pain, back ache and appetite improved after removal of cortical tumor the severe mental depression remained the same

CUSHING'S SYNDROME

Family history: Goiter

Past medical: Enuresis until 10 to 12 years of age

Chief complaint: Menstrual irregularity for 2 years

History of present illness: Periods were regular until 2 years before admission She then had amenorrhea for 5 months After injections periods returned at irregular intervals (2 to 3 weeks early or late) Injections stopped 3 months previously amenorrhea since Patient gained about 14 lbs during present illness mostly around the head and the trunk Hair growth increased on face only Her cheeks seemed to be purplish in color Excessive offensive sweating BP (systolic) from 165 to over 200 Dyspnea on climbing stairs and swelling of her ankles at night Headaches variable occasional blurring of vision and tinnitus Nocturia for 3 to 4 months frequency and burning past few weeks

PROTOCOL XXII CHART 25

Physical examination: Age 28, female, single Weight 140 lbs Height 63¼ in Pulse 80 BP 198/140 Obesity more marked around head and trunk extremities thin Cheeks are ruddy Facial hair increased Recent and old hemorrhages on lower left shin

Laboratory data: Urine essentially negative concentration 1014 RBC 5 730,000 Hgb 109% WBC 15 400 Differential polymorphonuclears 65% band forms 13%, lymphocytes 12% monocytes 10% Hematocrit 50.5% Platelet count 510 000 Bleeding time 3 min Coagulation time 18 min Clot retraction about 35% Prothrombin 92% of normal Resistometer normal NPN 34 mg % Total protein 8.0 Gm % Serum albumin 4.5 Gm % Serum globulin 3.5 Gm % Serum calcium 10.5 mg % Serum phosphorus 2.1 mg % Serum alkaline phosphatase 4.4 B U Serum acid phosphatase 140 units Serum potassium 15.1 mg % Serum sodium 140.0

poral region daily Total of 2,000 r to each side

Progress Four months later Return of menstrual periods Normal libido No bloating Feels well Weight 119 lbs without diet BP 120/100 standing 120/118 Skin eruptions cleared Striae fading RBC 4,800,000 Hgb 14.3 Gm WBC 8,000 Hematocrit 39% Total eosinophilic count 131/cu mm Fasting blood sugar 82 mg % Fasting serum phosphorus 4.0 mg % Sedimentation rate 70 mm/hr

REFERENCES

- 1 Albright F. Cushing's Syndrome: Its Pathological Physiology, Its Relationship to the Adrenogenital Syndrome and Its Connection with the Problem of the Reaction of the Body to Injurious Agents (Alarm Reaction of Selye). Harvey Lect (1942-1943) 38:123-186 (1943)
- 2 — Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 12th Meeting Feb 4-5 New York Josiah Macy Jr Foundation 1946 p 164
- 3 Albright F, Parson W, and Bloomberg L. Cushing's syndrome interpreted as hyperadrenocorticism leading to hyperglucocortecogenesis: results of treatment with testosterone propionate. *J Clin Endocrinol* 1:375-384 (May) 1941
- 4 Albright F, Reifenstein E C Jr and Forbes A P. Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 12th Meeting Feb 4-5 New York Josiah Macy Jr Foundation 1946 pp 148-177
- 5 Althausen T L, Lockhart J C and Soley M H. New diagnostic test (galactose) for thyroid disease. *Am J M Sc* 199:342-351 (Mar) 1940
- 6 Anderson E and Haymaker W. Prolonged survival of adrenalectomized rats treated with sera from Cushing's disease. *Science* 86:545-546 (Dec) 1937
- 7 — Adrenal cortical hormone (cortin) in blood and urine of patients with Cushing's disease. *Proc Soc Exper Biol & Med* 38:610-613 (June) 1938
- 8 Anderson E, Haymaker W and Joseph M. Hormone and electrolyte studies of patients with hyperadrenocortical syndrome (Cushing's syndrome). *Endocrinology* 23:398-402 (Oct) 1938
- 9 Anderson J. A case of polyglandular syndrome with adrenal hypernephroma and adenoma of the pituitary gland, both of small size. *Glasgow M J* 83:178-19 (1915)
- 10 de la Balze F A, Reifenstein E C Jr and Albright F. Differential blood counts in certain adrenal cortical disorders (Cushing's syndrome, Addison's disease and panhypopituitarism). *J Clin Endocrinol* 6:312-329 (Apr) 1946
- 11 Bauer J. Ueber Funktion des gesamten Nebennierensystems ohne anatomischen Befund. *Wien klin Wchnschr* 43:582-586 (May) 1930
- 12 — Zum heutigen Stand des Nebennierenproblems. *Deutsche med Wchnschr* 59:565-567 (Apr) 1933
- 13 — Was ist Cushing'sche Krankheit? *Schweiz med Wchnschr* 17:938-939 (Sept) 1936
- 14 — Die Pathophysiologie der Hypophyse. *Wien klin Wchnschr* 49:673-679 (May) 1936
- 15 Bauer W and Aub J C. Studies of calcium and phosphorus metabolism. XVI. The influence of the pituitary gland. *J Clin Investigation* 20:295-301 (May) 1941
- 16 Bennhold H. Die Therapie des Cushing Syndroms. *Wien Arch f inn Med* 35:101-124 (1941)
- 17 Bergstrand H. Luteinisierung der Ovarien bei einem Falle von basophilem Hypophysenadenom mit Cushing's Symptomenkomplex. *Arch f path Anat* 293:415-428 (1934)
- 18 Bishop P M and Close H O. Case of basophil adenoma of anterior lobe of the pituitary. Cushing's syndrome. *Guys Hosp Rep* 89:143-153 (Apr) 1932
- 19 Bland P B and Goldstein L. Pituitary basophilism: review of 42 verified cases with report of personal case. *Surg Gynec & Obst* 65:644-656 (Nov) 1937
- 20 Broster L R. Eight years experience with adrenal glands. *Arch Surg* 34:761-791 (May) 1937
- 21 — Surgery of adrenal cortex. *Brit J Sur* 26:925-941 (Apr) 1939
- 22 Browne J S L, Vennart E H et al. Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing Symposium on Urinary Corticosteroids 10th Meeting June 15-16 New York Josiah Macy Jr Foundation 1945 pp 131-219
- 23 Butler G C and Marnan J F. Isolation of pregnane 3:17:20 triol from urine of women showing adrenogenital syndrome. *J Biol Chem* 119:565-572 (July) 1937
- 24 Cantarow A. Urine chloride concentration in patients with Cushing's syndrome. *Science* 90:375-376 (Oct) 1939
- 25 Clutton H E Jr, Bennett W A, Power M H and Kepler E J. Cushing's syndrome without adenomatous or hyperplastic changes in pituitary body or adrenal cortices and complicated by alkalosis: report of case with necropsy. *J Clin Endocrinol* 5:61-69 (Feb) 1945
- 26 Cohen H and Dible J H. Pituitary basophilism associated with basophil carcinoma of anterior lobe of pituitary gland. *Brain* 59:395-407 (Dec) 1936
- 27 Collip J B. Corticotropic (adrenotropic) thyrotropic and parathyrotropic factors. *JAMA* 115:2073-2079 (Dec) 1940
- 28 Corcoran A C. The Renal Pressor System and Experimental and Clinical Hypertension. Recent Advances in Hormone Research Vol 3. New York Acad Press 1948 pp 325-341
- 29 Costello R T. Subclinical adenoma of pituitary gland. *Am J Path* 12:205-216 (Mar) 1936
- 30 Craig J and Cran B S. Basophil adenoma of pituitary gland. *Quart J Med* 3:57-67 (Jan) 1934

steroids 16.8 mg/24 hrs Bone marrow—increased fat, otherwise normal After roentgen therapy (unimproved), serum potassium 14.2 mg % and chlorides 100 mEq/l Glucose tolerance test (blood sugar mg %) fasting 86, ½ hr, 243, 1 hr, 264 2 hrs 218 Etamon test marked response with no blood pressure in sitting position EKG—marked LAD and inversion T₁ and T

Röntgenographic findings Skull—osteoporosis, posterior clinoids thin, depression of sella into floor of sphenoid sinus, lateral contour area of sella was 150 sq mm, loss of lamina dura Pyelograms—normal, left kidney lower than right Chest—fracture of several ribs with callous formation Legs—osteoporosis, numerous growth lines

Treatment Patient received 2 series roentgen therapy—total 2,000 r over pituitary. No change in condition Hemorrhagic ulcer on skin Hospitalized Bilateral partial adrenalectomy attempted, cardiac arrest, necessitating massaging of the heart recovery Three weeks later uneventful bilateral hemi adrenalectomy (Dr R B Cattell) Adrenals appeared hyperplastic however,

weight of removed tissue was 4.3 Gm Microscopic—normal adrenal tissue

Progress Two years after operation general condition satisfactory, except for blood pressure which after a few months returned to values around 180/140 when she did not take potassium thiocyanate, otherwise it was down to 140/100 Gallop rhythm and nocturnal dyspnea did not return Back or leg pain relieved No ecchymotic tendency Menstruation followed when given progesterone sublingually for 5 day periods Total eosinophil count was 100/cu mm 1 year after operation and declined gradually to 25/cu mm 1 year later Lymphocytes 16%

Comment This case illustrates persistent hypertension when symptomatically and otherwise there has been general improvement The hypertensive family anlage may be a predisposing factor Other treatments as testosterone, low salt and high protein diet ammonium chloride may have contributed a little to her well being Potassium thiocyanate 6 to 9 gr a day, had the most marked effect on her blood pressure

CUSHING'S DISEASE WITH AN ENLARGED SELLA · PROTOCOL XXIV FIG 102

Family history Negative

Past medical Married 8 years No children

Husband alcoholic

Chief complaint Bloating

History of present illness Seven months before admission patient noted frontal headaches and slight gain in weight (Weighed 86 lbs at marriage) Six weeks before entry she had marked bloating puffiness of eyes and blurred vision Headaches ceased with onset of edema Hypertension discovered 3 weeks before admission Given an injection which caused marked diuresis Amenorrhea for 2 months

Physical examination Age 28 female married Weight 132 lbs Height 56 in BP 145/90 160/120 Buffalo type of obesity pig eyed and moon face Purplish striae on abdomen Acneform and seborrheic eruptions near hair line chest and back Hirsutism of face and chin

Laboratory data Urine: albumin 1 plus sugar trace specific gravity 1.003 RBC

5,420,000 Hgb 16.8 Gm WBC 5,200 Hematocrit 52% Serum calcium 9.7 mg % Serum phosphorus 3.1 mg % BMR plus 2% Sedimentation rate 57 mm/hr

GLUCOSE TOLERANCE TEST

Hour	Serum		Urine Sugar
	Blood Sugar	Inorganic Phosphorus	
	mg %	mg %	
0	117	4.0	0
½	235	4.0	Trace
2	233	2.5	6.3%
3	267	2.9	6.0%

Röntgenographic findings Skull—thin cranial vault no decalcification sella 152 sq mm floor of fossa destroyed and right posterior clinoid process Pelvis—no osteoporosis Arteriosclerosis of pelvic vessels No displacement of kidneys

Treatment Irradiation 200 r to each tem

- ous adrenal cortical principles on insulin hypoglycemia and liver glycogen *J Biol Chem* 135 511 517 (Sept.) 1940
- 68 Hall G Kellett C E and Stephenson G R Cushing's syndrome report of case in which no endocrine tumour was found *Lancet* 1 862 865 (Apr.) 1939
 - 69 Hanssen P Cushing syndrome report of a case treated with x ray *Acta med Scandinav* 89 517 525 1936
 - 70 Harri M F Personal communication
 - 71 Haymaker W and Anderson E Syndrome arising from hyperfunction of adrenal cortex adrenogenital and Cushing's syndromes—review *Internat Clin* 4 244 299 (Dec.) 1938
 - 72 Heinbecker P Pathogenesis of Cushing's syndrome *Medicine* 23 225 247 (Sept.) 1944
 - 73 — Cushing's syndrome *Ann Surg* 124 252 261 (Aug.) 1946
 - 74 Hochman A Cushing's syndrome *Acta med orient* 3 19 25 (Jan Feb.) 1943
 - 75 Hofmann A Ein Fall von Morbus Cushing mit Genitalblutungen *Klin Wchnschr* 14 1582 1584 (Nov.) 1935
 - 76 Horneck K Zur Klinik des Morbus Cushing *Ztschr f klin Med* 129 191 197 (Nov.) 1935
 - 77 Hoyle C and Wall C Adrenogenital syndrome (Cushing type) *Proc Roy Soc Med* 27 395 397 1933 1934
 - 78 Hurxthal L M Unpublished data
 - 79 Ingle D J Production of glycosuria in normal rat by means of 17 hydroxy 11 dehydrocorticosterone *Endocrinology* 29 649 652 (Oct.) 1941
 - 80 — Some studies on the role of the adrenal cortex in organic metabolism *Ann New York Acad Sc* 50 576 596 (June) 1949
 - 81 Ingle D J and Thorn G W Comparison of effects of 11 desoxycorticosterone acetate and 17 hydroxy 11 dehydrocorticosterone in partially depancreatized rats *Am J Physiol* 132 670 678 (Apr.) 1941
 - 82 Jacobi J, and Tigges F Zur Pathogenese des Cushing Syndroms München med Wchnschr 86 1665 1667 (Nov.) 1939
 - 83 Jamin F Die hypophyse are Plethora (Cushing'sche Krankheit pituitary basophilism) München med Wchnschr 81 1045 1085 (July) 1934
 - 84 Jores A Über Hormonuntersuchungen bei Morbus Cushing *Klin Wchnschr* 14 1343 1351 (Sept.) 1935
 - 85 — Die Bedeutung der Hypophyse für die Entstehung des Hochdruckes insbesondere der essentiellen Hypertonie *Klin Wchnschr* 15 841 846 (June) 1936
 - 86 Kehrer M Das Syndrom von Cushing seine Analyse und Synthese *Ergebn d inn Med u Kinderh* 55 178 211 1938
 - 87 Kendall E C Hormones of adrenal cortex *Endocrinology* 30 853 860 (June) 1942
 - 88 — The chemistry and partial synthesis of adrenal steroids *The adrenal cortex* *Ann New York Acad Sc* 50 540-547 (June) 1949
 - 89 Kenyon A T Gallagher T F, Peterson D H Dorfman R I and Koch F C The urinary excretion of androgenic and estrogenic substances in certain endocrine states studies in hypogonadism gynecomastia and virilism *J Clin Investigation* 16 705 717 (Sept.) 1937
 - 90 Kepler, E J Report of four cases *Proc Staff Meet Mayo Clin* 8 102 107 1933
 - 91 — Relationship of Crooke's changes in basophilic cells of anterior pituitary body in Cushing's syndrome (pituitary basophilism) *J Clin Endocrinol* 5 70 75 (Feb.) 1945
 - 92 — Cushing's disease a primary disorder of the adrenal cortices *Ann New York Acad Sc* 50 657 678 (June) 1949
 - 93 Kepler E J Dockerty M B and Priestley J T Adrenal like tumor associated with Cushing's syndrome (so called masculinoblastoma luteoma hypernephroma adrenal cortical carcinoma of ovary) *Am J Obst & Gynec* 47 43 62 (Jan.) 1944
 - 94 Kepler E J and Keating F R Jr Diseases of adrenal glands tumors of adrenal cortex, diseases of adrenal medulla and allied disturbances *Arch Int Med* 68 1010-1036 (Nov.) 1941
 - 95 Kepler E J Sprague R G Clavett O T Power M H Mason H L and Rorer H M Adrenal cortical tumor as caused with Cushing's syndrome *J Clin Endocrinol* 4 499 531 (July) 1948
 - 96 Kessel F K Morbus Cushing Ein Überblick über Klinik und Kasuistik des basophilen Hypophysenadenoms *Ergebn d inn Med u Kinderh* 50 620-678 1936
 - 97 Kraus E J Zur Frage der Bildungswirkung der übergeordneten Geschlechtshormone im Hypophysenvorderlappen (Zugleich ein Beitrag zur Morphologie der Hypophyse bei pathologischen Proliferauscheidern) *Beitr z path Anat u z allg Path* 91 245 275 1933
 - 98 Lawrence J H and Zimmerman H M Pituitary basophilism report of case *Arch L Med* 55 745 759 (May) 1933
 - 99 Lawrence R D Discussion on suprarenal and pituitary tumours and their correlation with experimental findings *Proc Roy Soc Med* 27 275 277, 1933 1934
 - 100 Leary D C and Zimmerman H M Basophil infiltration in neurohypophysis *Am J Path* 13 213 228 (Mar.) 1937
 - 101 Lendvai J Ein Fall von Cushing'schem Syndrom symptomfrei nach Parathyreoidectomie *Abhandlung Wien Klin Wchnschr* 49 749 753 (June) 1936
 - 102 Lescher F G and Robb Smith A H Comparison of pituitary basophilic syndrome and adrenal corticogenital syndrome with report on pathology *Quart J Med* 4 23-33 (Jan) 1935
 - 103 Levy M S Power M H and Kepler E J The specificity of the water test as a diagnostic procedure in Addison's disease *J Clin Endocrinol* 6 607 632 (Sept.) 1946
 - 104 Lewis L A and Page I H Studies on the protective power of adrenal extract and steroids against bacterial toxins in adrenalectomized rats *Ann New York Acad Sc* 50 547 551 (June) 1949
 - 105 Leyton O Multiglandular disease (Scherstein lecture) *Lancet* 1 1221 1226 (June) 1934
 - 106 Leyton O Turnbull H M and Bratton A B Primary cancer of thymus with pluriglandular disturbance *J Path & Bact* 34 635 660 (Sept.) 1931
 - 107 Lüsner P Ueber die Beziehungen zwischen Nebenmieren und Körper wachstum besonders Riesenwuchs *Beitr z klin Chir* 37 282 306 1903
 - 108 Lüsner H Relation of the Cushing syndrome to the pars intermedia of the hypophysis *Tr A. Am Physicians* 50 110 1935

- 31 Crile N, Turner H, and McCullagh F P Polyglandular disease New York State J Med 36 475-484 (Apr) 1936
- 32 Crooke A C Change in basophil cells of pituitary gland common to conditions which exhibit syndrome attributed to basophil adenoma J Path & Bact 41 339-349 (Sept) 1935
- 33 — Basophilism treated unsuccessfully with massive doses of oestrogens and deep x ray therapy but cured by radon seeds inserted into the sella turcica Proc Roy Soc Med 40 153 (Nov) 1946
- 34 — The endocrine disorders associated with Cushing's syndrome and virilism J Clin Endocrinol 7 787-794 (Dec) 1947
- 35 Crooke A C and Callow R K Differential diagnosis of forms of basophilism (Cushing's syndrome) particularly by estimation of urinary androgens Quart J Med 8 233-249 (July) 1939
- 36 Cushing H Pituitary Body and Its Disorders Philadelphia Lippincott 1912 pp 217-219
- 37 — Basophil adenomas of pituitary body and their clinical manifestations (pituitary basophilism) Bull Johns Hopkins Hosp 50 137-195 (Mar) 1932
- 38 — Dy pituitarism? 20 years later with special consideration of pituitary adenomas Arch Int Med 51 487-557 (Apr) 1933
- 39 Cuttner W C Cox A J Jr, and Laqueur G L Cushing's syndrome and related conditions Stanford Bull 3 1-12 1945
- 40 Dattner B Zwei Fälle von Cushing'schem Adenom Wien klin Wchnschr 1 809-810 (May) 1935
- 41 Daughaday W H, Jaffe H and Williams R H Adrenal cortical hormone excretion in endocrine and nonendocrine disease as measured by chemical assay J Clin Endocrinol 8 244-256 (Mar) 1948
- 42 Daughaday W H and MacBryde C M Studies of urinary steroid excretion during salt deprivation and administration of DCA and ACTH Proc of the First Clinical Conference ed J R Mote Philadelphia Blakiston 1950 pp 148-157
- 43 Deakins M L, Friedgood H M, and Ferrebee J W Some effects of testosterone, testosterone propionate, methyl testosterone, stilbestrol and x ray therapy in patient with Cushing's syndrome J Clin Endocrinol 4 376-384 (Aug) 1944
- 44 Delachaux A Étude clinique des régulations hypophysaires dans un syndrome de Cushing Schweiz med Wchnschr 21 760-763 (Aug) 1940
- 45 Dorfman R I, Wilson H M, and Peters J P Differential diagnosis of basophilism and allied conditions Endocrinology 27 1-15 (July) 1940
- 46 Draps D G and Osterberg A E Evaluation of colorimetric and biologic method for determining urinary androgens Endocrinology 27 345-354 (Sept) 1940
- 47 Dunn C W The Cushing Syndrome Endocrinology 33 374-385 (Mar) 1938
- 48 Ecker A D The hyaline change in the basophil cells of the pituitary body not associated with basophilism Endocrinology 23 609-617 (Nov) 1938
- 49 — Anatomic associations of pituitary basophilism Proc Staff Meet Mayo Clin 14 200-202 (Mar) 1939
- 50 Eichenhardt L, and Thompson K W Brief consideration of present status of so called pituitary basophilism with tabulation of verified cases Yale J Biol & Med 11 507-522 (May) 1939
- 51 Escamilla E F Diagnostic significance of urinary hormonal assays: report of experience with measurements of 17 ketosteroids and follicle stimulating hormone in the urine Ann Int Med 30 249-290 (Feb) 1949
- 52 Ewen (Demonstration) Klin Wchnschr 16 1661 (Nov) 1937
- 53 Farber J E, Guftina F J, and Potoloff A V Cushing's syndrome in children: review of literature and report of case Am J Dis Child 65 593-603 (Apr) 1943
- 54 Forbes W Carcinoma of the pituitary gland with metastases to the liver in a case of Cushing's syndrome J Path & Bact 59 137-144 (Jan-Apr) 1947
- 55 Fox T C A case of primary sarcoma of the left suprarenal capsule with extensive thrombosis of the vena cava inferior in a child (Specimens) Tr Path Soc London 36 460-463 (Apr) 1885
- 56 Frazer H W, Albright F, and Smith P H Value of glucose tolerance test, insulin tolerance test and glucose insulin tolerance test in diagnosis of endocrinologic disorders of glucose metabolism J Clin Endocrinol 1 297-306 (Apr) 1941
- 57 Fraser R W, Forbes A P, Albright F, Sulzowitch H, and Reifenstein E C Colorimetric assay of 17 ketosteroids in urine: survey of use of this test in endocrine investigation, diagnosis and therapy J Clin Endocrinol 1 234-256 (Mar) 1941
- 58 Freyberg R H, Barker P E, Newburgh L H, and Collier F A Pituitary basophilism (Cushing's syndrome): report of verified case with discussion of differential diagnosis and treatment Arch Int Med 58 187-212 (Aug) 1936
- 59 Freyberg R H and Grant R L Calcium and phosphorus metabolism in verified case of pituitary basophilism Arch Int Med 58 213-228 (Aug) 1936
- 60 Freyberg R H and Newburgh L H Obesity and energy exchange in verified case of pituitary basophilism Arch Int Med 58 229-234 (Aug) 1936
- 61 Fuller C J and Russell D B Chromophobe adenoma of pituitary associated with Cushing's syndrome with histological report Lancet 2 181-183 (July) 1935
- 62 Gellerstedt N Endokrin wäskame Hypofyse tumoren Acta path et microbiol Scand (suppl) 38 63-80 1938
- 63 Gill A M Treatment of Cushing's syndrome with large doses of oestrogen Lancet 2 70-72 (July) 1937
- 64 Goettsche H Über die Ausscheidung des Hypophysenorderlappensekretionshormons und des Follikelhormons im Urin beim Cushing'schen Syndrom Arch f Gynak 170 332-341 1940
- 65 — Zur Entstehung der Störungen der weiblichen Genitalfunktion bei der Cushing'schen Krankheit Wien med Wchnschr 90 571-572 (Aug) 1940
- 66 Goldzieher M A Adrenal cortical disturbances Internat Clin 4 20-39 (Dec) 1939
- 67 Grattan J F, and Jensen H Effect of pituitary adrenocorticotrophic hormone and of vari-

- l'étude des tumeurs hypophysaires *Presse méd* 41 1799 1804 (Nov) 1933
- 151 Russell D S Evans H and Crooke A C Two cases of basophil adenoma of pituitary gland *Lancet* 2 240 246 (Aug) 1934
 - 152 Rutishauser E Osteoporotische Fettsucht (Pituitary Basophilism) *Deutsche Arch f klin Med* 175 640 680 (May) 1933
 - 153 Salter W T Humm F D Oesterling M J and Engstrom W W Urinary steroid balance in virilism and hypogonadism Assoc Study Int Secretions Program of 29th Meeting June 1947 p 17
 - 154 Salus F Zur Kenntnis der malignen Hypophyseadenome *Ztschr f d ges Neurol u Psychiat* 148 574 583 1933
 - 155 Sansone I Sindromi tipo Cushing (studio clinico e considerazioni patogenetiche) *Arch sc med* 64 681 712 (Dec) 1937
 - 156 Schenker V and Brown J S Protein Anabolic Activity of Steroid Compounds (Fr C Reifenstein) New York Josiah Macy Jr Foundation 1942 pp 44-45
 - 157 Schmidt C Beitrag zum Cushingschen Syndrom *Klin Wchnschr* 15 1437 1443 (Oct) 1936
 - 158 Schneeberg N G LaKoff W B and Meranze D R Evaluation of blood test for galactose tolerance in diagnosis of hyperthyroidism *Arch Surg* 46 581 588 (Apr) 1943
 - 159 Selye H and Hall C E Pathologic changes induced in various species by overdosage with desoxycorticosterone *Arch Path* 36 19 31 (July) 1943
 - 160 Sendraï M and Tamalet L J Le test hypophysaire d'Aron en climax *Toulouse méd* 40 1 15 (Jan) 1939
 - 161 Simpson S L Major Endocrine Disorders *Johns Hopkins Med Pub* 1933 p 70
 - 162 Simpson S L de Fremery P and Macbeth A The presence of an excess of male (comb growth and prostate stimulating) hormone in virilism and pseudo hermaphroditism *Endocrinology* 20 363 372 (May) 1936
 - 163 Soffer L J Clinical manifestations of adrenal cortical hyperfunction *Bull New York Acad Med* 23 479 493 (Aug) 1947
 - 164 Soffer L J Leswick G Sorkin S Z Sobotka H H and Jacobs M The utilization of intravenously injected salt in normals and in patients with Cushing's syndrome before and after administration of desoxycorticosterone acetate *J Clin Investigation* 23 51 54 (Jan) 1944
 - 165 Sommer F Plüvinglanduläre Störungen *Klin Wchnschr* 16 1389 1937
 - 166 Sosman M C Irradiation in treatment of pituitary adenomas *Proc Interst Postgrad M A North America* October 1937 pp 239 246
 - 167 — Cushing's disease pituitary basophilism *Am J Roentgenol* 62 1 32 (July) 1949
 - 168 Spence H M and Thompson M G Jr Hormone producing tumor of adrenal cortex with congenital absence of contralateral adrenal gland report of a case *New England J Med* 236 13 20 (Jan) 1947
 - 169 Sundermann A Ein Beitrag zum Morbus Cushing (Cushing Syndrom bei hypophysärem Zwergwuchs vergesellschaftet mit Chlorosyphrophie) *Endokrinologie* 23 17 32 1940
 - 170 Susman W Pituitary adenoma *Brit M J* 2 1215 1933
 - 171 — Adenomata of pituitary with special reference to pituitary basophilism of Cushing *Brit J Surg* 22 539 544 (Jan) 1935
 - 172 Sussman M L and Copleman B Roentgenographic appearance of bones in Cushing's syndrome *Radiology* 39 288 292 (Sept.) 1942
 - 173 Talbot N B Albright F Saltzman A H Zygmuntowicz A and Wixom R The excretion of 11 oxycortico steroid like substances by normal and abnormal subjects *J Clin Endocrinol* 7 331 351 (May) 1947
 - 174 Talbot N B Butler A M and MacLachlan E A A Alpha and beta neutral ketosteroids (androgens) preliminary observations on their normal urinary excretion and clinical usefulness of their assay in differential diagnosis *New England J Med* 223 369 373 (Sept) 1940
 - 175 Talbot N B and Reifenstein E C Jr Conference on Metabolic Aspects of Coma and Convulsions Including Bone and Wound Healing 13th Meeting June 10 11 New York Josiah Macy Jr Foundation 1946 pp 111 118
 - 176 Teel H M Basophilic adenoma of hypophysis with associated pluriglandular syndrome report of case *Arch Neurol & Psychiat* 26 593 599 (Sept) 1931
 - 177 Tessauro H Zur Kasuistik und Pathologie der Cushingschen Krankheit *Endokrinologie* 18 319 394 1937
 - 178 Thompson K W and Eisenhardt L Further consideration of Cushing syndrome *J Clin Endocrinol* 3 445 452 (Aug) 1943
 - 179 Thorn G W Engel L L and Lewis R A Effect of 17 hydroxycorticosterone and related adrenal cortical steroids on sodium and chloride excretion *Science* 94 348 349 (Oct.) 1941
 - 180 Thorn G W Engel L L and Eisenhardt H Effect of corticosterone and related compounds on renal excretion of electrolytes *J Exper Med* 68 161 171 (Aug) 1938
 - 181 Thorn G W Koepf G F Lewis R A and Olsen E F Carbohydrate metabolism in Addison's disease *J Clin Investigation* 19 813 832 (Nov) 1940
 - 182 Turney H G Discussion on disease of the pituitary body *Proc Roy Soc Med (Sec Neuro & Ophthal)* 6 69 78 (Mar) 1913
 - 183 Ulrich H L Pituitary basophilism without adenomata anywhere *Minnesota Med* 19 535 537 (Aug) 1936
 - 184 Urban H In Fall von Basophilismus (Morbus Cushing) *Wien klin Wchnschr* 50 1122 1126 (July) 1937
 - 185 Van Buchem H S Die Cushingsche Krankheit *Acta med Scandinav* 108 544 560 1942
 - 186 Venning E H and Browne J S L Excretion of glycocholic corticoids and of 17 ketosteroids in various endocrine and other disorders *J Clin Endocrinol* 7 79 101 (Feb) 1947
 - 187 Walters W Walder R M and Kepler E J Suprarenal cortical syndrome with presentation of 10 cases *Ann Surg* 100 670 688 (Oct) 1934
 - 188 — Suprarenal cortical syndrome report of 2 cases with successful surgical treatment *Proc Staff Meet Mayo Clin* 9 400 407 (July) 1934
 - 189 Weber F P Cutaneous striae purpura high blood pressure amenorrhoea and obesity of type sometimes connected with cortical tumours of adrenal glands occurring in absence of any such tumour morphogenetic and hormonal effects of true hypernephromata of

- 109 ——— Successful removal of adrenal cortical tumor causing sexual precocity in a boy 5 years of age *Tr A Am Physicians* 48 274 235 1933
- 110 Long C N Discussion of mechanism of action of adrenal cortical hormones on carbohydrate and protein metabolism *Endocrinology* 30 8-853 (June) 1942
- 111 Long C N Fry E G and Thompson K W The effect of adrenalectomy and adrenal cortical hormones upon pancreatic diabetes in the rat *Am J Physiol* 123 130 131 1938
- 112 Long C N Katzin B and Fry E G Adrenal cortex and carbohydrate metabolism *Endocrinology* 26 309 344 (Feb.) 1940
- 113 Lozner E L Winkler A W Taylor F H and Peters J P Intravenous glucose tolerance test *J Clin Investigation* 20 50 515 (Sept.) 1941
- 114 Luft R Study on hereditary Cushing's syndrome and precocious puberty *Acta med Scandinav (suppl)* 149 1 119 1944
- 115 ——— Diagnosis of Addison's disease in women *Nord Med (Higies)* 12 3258 3261 (Nov) 1941
- 116 ——— The treatment of Cushing's syndrome *Acta med Scandinav* 124 227 251 1946
- 117 Lukens F D Flippin H J and Thorpe F M Adrenal cortical adenoma with absence of opposite adrenal report of case with operation and autopsy *Am J M Sc* 193 812 818 (June) 1937
- 118 MacCallum W G Fletcher T B Duff G L and Ellsworth R Relation of Cushing syndrome to pars intermedia of hypophysis *Johns Hopkins Hosp Bull* 56 350 365 (June) 1935
- 119 ——— Relation of the Cushing syndrome to the pars intermedia of the hypophysis *Tr A Am Physicians* 50 194 212 1935
- 120 MacLay W S Stokes A B and Russell D S Mental disorder in Cushing's syndrome with pathological report *J Neurol & Psychiat* 1 110 119 (Apr.) 1933
- 121 Malaguzzi Valeri C Über den Cushing'schen Symptomenkomplex *Ergebn d inn Med u Kinderh* 58 29 77 1940
- 122 Maranon G Sur la pathogénie du syndrome de Cushing *Ann d'endocrinol* 1 241 256 (July) 1939
- 123 Margen S Is the protein metabolic abnormality of Cushing's syndrome catabolic or anti-anabolic? *Assoc Study Int Secretions* pp 22 23 (June) 1949
- 124 McCullagh E P quoted by Selye H Textbook of Endocrinology *Acta Endocrinologica* p 309 Montreal Canada Université de Montréal 1947
- 125 McCullagh E P and Balga H V Bioassays for urinary androgens comparison of results in normal men with those having endocrine disturbances *Endocrinology* 25 753 764 (May) 1940
- 126 McLetchie N G Pituitary basophilism syndrome of Harvey Cushing *J Endocrinology* 3 332 346 (May) 1944
- 127 McQuarrie I Johnson R M and Ziegler M R Plasma electrolyte disturbance in patient with hypercortico adrenal syndrome contrasted with that found in Addison's disease *Endocrinology* 21 761 772 (Nov.) 1937
- 128 Melligren J Beitrag zur Pathologie der Hypophyse bei Interrenalismus *Beitr z path Anat u z allg Path* 106 487 520 1942
- 129 Meyler L and Hommes M Adrenal cortical syndrome *Acta med Scandinav* 93 251 264 1937
- 130 Neff F C Tice H M Walker G A and Ockerblad N Adrenal tumor in female infant with hypertrichosis hypertension over development of external genitalia obesity but absence of breast enlargement *J Clin Endocrinol* 2 125 127 (Feb.) 1942
- 131 Norris E H Arrhenoblastoma malignant ovarian tumor associated with endocrinological effects *Am J Cancer* 32 1 29 (Jan.) 1938
- 132 Oppenheimer H S Globus J H Silver S and Shaskan D Suprarenal virilism and Cushing's pituitary basophilism *Tr A Am Physicians* 50 371 387 1935
- 133 Page A P Roberts L V and Biggart J H Cushing's syndrome in mulatto with histological report *Lancet* 2 625 627 (Sept.) 1937
- 134 Parade Morbus Cushing *Klin Wchnschr* 17 901 902 1935
- 135 Pardee I Basophilic hyperplasia of pituitary in essential hypertension *Am J M Sc* 190 1 8 (Jul.) 1935
- 136 ——— Pituitary basophilism of Cushing syndrome of basophilic adenoma *Bull Neurol Int New York* 6 183 198 (Aug.) 1937
- 137 ——— Basophilic syndrome of pituitary pituitary basophilism (Cushing) *Arch Neurol & Psychiat* 31 1007 1025 (May) 1934
- 138 Pattison A R and Swan W G Surgical treatment of pituitary basophilism *Lancet* 1 1265 1269 (June) 1938
- 139 Pennington G A and Kaye Scott R Pituitary basophilism *Lancet* 2 684 686 (Nov.) 1947
- 140 Perloff W H Rose E and Sunderman F W Therapeutic observations in Cushing's syndrome effect of various agents on calcium phosphorus and nitrogen excretion in patient with pituitary basophilism *Arch Int Med* 72 494 505 (Oct.) 1943
- 141 Pratt J P and Schaefer R L Sex precocity virilism adrenal cortical tumor *Am J Obst & Gynec* 49 623 633 (May) 1945
- 142 Pritchard E A Pituitary basophilism *Proc Roy Soc Med* 27 673 675 (Apr.) 1934
- 143 Rakoff A E Cantaron A and Paschalis K E Cushing's syndrome 2 cases treated with stilbestrol *J Clin Endocrinol* 1 912 913 (Nov) 1941
- 144 Rasmussen A T Relation of basophilic cells of human hypophysis to blood pressure *Endocrinology* 20 673 678 (Sept.) 1936
- 145 Rasmussen A T and Nelson A A Pars intermedia basophil adenoma of hypophysis *Am J Path* 14 297 310 (May) 1938
- 146 Reifenstein E C Jr Personal communication
- 147 ——— Conference on Metabolic Aspects of Convalescence, Including Bone and Wound Healing 5th Meeting Oct 8 9 New York Josiah Macy Jr Foundation 1943 pp 79 83
- 148 Reifenstein E C Jr Forb A P Albright F Donaldson E and Carroll E Effect of methyltestosterone on urinary 17 ketosteroids of adrenal origin *J Clin Investigation* 24 416 434 (July) 1945
- 149 Reuss L Sigmar M and Röllner D Mineral salzlar bei einem Fall von M Cushing und Versuch einer Behandlung mit hohen Follikulindosen *Wien klin Wchnschr* 52 554 561 (June) 1939
- 150 Roussy G and Oberling C Contribution à



FIG 95 CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 96 and 99) Bedridden because of extreme weakness and pain in back. Note striae of trunk, normal or excess hair, adequate beard, buffalo obesity. Scars from adrenal exploration. This man's disorder began during solitary confinement when he developed great thirst, gain in weight and purplish striae on a diet of bread, water and an occasional stew. Is this the alarm reaction without counterreaction? (See Adaptation Syndrome)



FIG 96 CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 95-97) Striae on legs of patient shown above

- adrenal cortex *Brit J Dermat* 58 1 19 (Jan) 1956
- 190 Wells B H and Kendall F C Influence of adrenal cortex in phlorhazum diabetes *Proc. Staff Meet Mayo Clin* 15 565 573 (Sept) 1940
- 191 Westman A Differentialdiagnostische Probleme bei virilisierenden Erkrankungen der Frau *Acta obst et gynec Scandinav* 19 455 4 6 1939
- 192 White A and Dougherty T F Influence of hormones on lymphoid tissue structures and function The role of pituitary adrenotropic hormone in the regulation of the lymphocytes and other cellular elements of the blood *Endocrinology* 35 1 14 (July) 1944
- 193 Whitelaw M J Case of Cushing's syndrome treated with testosterone propionate *J Clin Endocrinol* 4 480-482 (Oct) 1944
- 194 Wirth Pedersen G Case of suprarenal tumor and of hypophyseal tumor both with striae distensae cutis llo pituitud 74 1231 1244 1931
- 195 Wilhelm S F and Gross S Surgical removal of adrenal adenoma with relief of Cushing's syndrome *Am J M Sc* 207 196 204 (Feb) 1944
- 196 Wilkins L Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 12th Meeting Feb 4 5 New York Josiah Macy Jr Foundation 1946 p 29
- 197 — A feminizing adrenal tumor causing gynecostasia in a boy of five years contrasted with a virilizing tumor in a five year old girl *J Clin Endocrinol* 8 111 132 (Feb) 1948
- 198 Wilkins L and Fleischmann W Influence of various androgenic steroids on nitrogen balance and growth *J Clin Endocrinol* 6 382-401 (May) 1946
- 199 Wilkon D M Fowler M H and Kepler E J Alkalosis and low plasma potassium in a case of Cushing's syndrome a metabolic study *J Clin Investigation* 19 701 707 (Sept) 1940
- 200 Wohl M G Moore J R and Young B R Basophilic adenoma (pituitary basophilism) report of case with clinical improvement of systemic manifestations after irradiation of pituitary *Radiology* 24 53 57 (Jan) 1935
- 201 Wright C A Pituitary basophilism discussion of additional factors in relation to 4 cases *M Rec* 141 191 196 (Feb) 1935



FIG 95 CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 96 and 99) Bedridden because of extreme weakness and pain in back Note striae of trunk normal or excess hair adequate beard buffalo obesity Scars from adrenal exploration This man's disorder began during solitary confinement when he developed great thirst gain in weight and purplish striae on a diet of bread water and an occasional stew Is this the alarm reaction without counterreaction? (See Adaptation Syndrome)



FIG 96 CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 95 97) Striae on legs of patient shown above

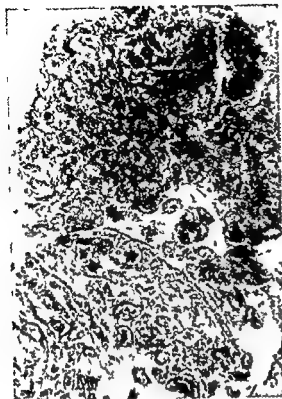


FIG 9: TESTICULAR ATROPHY IN CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 95 96)



FIG 98 CUSHING'S SYNDROME (See Protocol 11 \ \) Weakness rapid increase in weight and mental depression for 1 year Buffalo obesity Striae on thighs buttocks axillae and groins Testes small Adequate beard Benign adrenocortical tumor removed without improvement

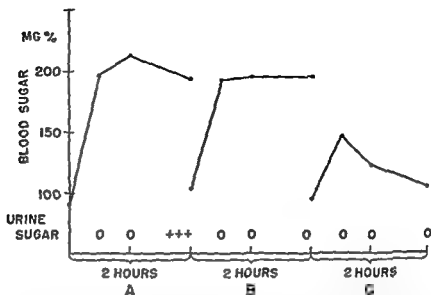


CHART 25 ORAL GLUCOSE TOLERANCE AND GLUCOSE INSULIN TOLERANCE TESTS IN CUSHING'S DISEASE (See Protocol 11 XXII) (A) Glucose tolerance test showing diabetic curve (B) Insulin glucose tolerance test showing essentially no effect on hyperglycemia. No glycosuria suggesting that insulin has raised renal threshold (increased phosphorylation) (C) Normal glucose tolerance test 1 year later. Roentgen ray treatments over pituitary with improvement

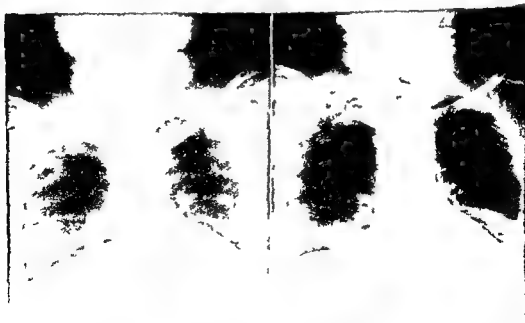


FIG 99 CUSHING'S SYNDROME (See Protocol 11 XXIII Fig 100 Chart 137) (Left) Pathologic fractures of ribs with callous formation (Right) Healed 4 months later. These films show that despite osteoporosis local injury is sufficient to overcome antianabolic or catabolic influences in this disorder

FIG 100 CUSHING'S SYNDROME (See Protocol 11 XVIII Fig 99 Chart 13.) (Right) Advanced case showing the moon face the typical plethoric obesity and purplish striae. Five years before admission patient noted an increase in weight (42 lbs) and change in body contour. Hirsutism and headaches. Irregular menstruation was followed by amenorrhea. Weakness and pains in legs ensued. Finally, paroxysmal nocturnal dyspnea and ankle edema. BP 190/130. Gallop rhythm. Urine negative. Hgb 15, Gm. NPN 48 mg %. Sella enlarged unilaterally with depression into floor. Vault osteoporotic with loss of periodontal membranes. Several rib fractures. Osteoporosis of all bones. Fasting blood sugar 111 mg %. Serum calcium 10.5 mg %. Serum phosphorus 2.2 mg %. Alkaline phosphatase 3.6 IU. Urograms negative. Little effect from 2 courses of roentgenotherapy. Bilateral subtotal adrenalectomy performed. Temporary fall in blood pressure. General improvement. Loss of back pain. Ecchymoses of legs. Nocturnal dyspnea. Menstrual periods with oral progesterone therapy. BP maintained at lower levels with sedatives or potassium thiocyanate. Patient has no complaints 2 years after operation.

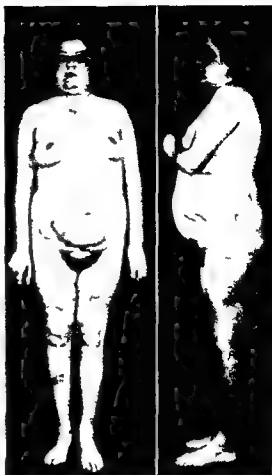


FIG 100 CUSHING'S SYNDROME *Continued* Facial appearance before therapy and two years later

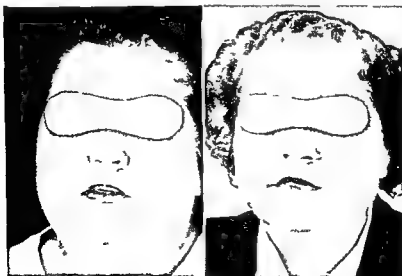




FIG 101 CUSHING'S SYNDROME—CHANGE IN FACIAL CONTOUR AFTER THERAPY *Chief complaints* Swelling of face and ankles for 5 months Facial hair growth and weakness of her legs *History of present illness* Patient developed a craving for salt and crackers Ammonium chloride was administered without benefit Menstrual periods were regular but decreased gradually in amount Ecchymoses occurred on her arms with slight trauma Weight 157 lbs a gain of 7 lbs *Physical examination* Age 47 female Moon face Ecchymotic spots on arms and face No striae BP 210/120 Pitting edema of ankles Marked muscular weakness patient has to pull herself up with her arms from a sitting position *Laboratory data* RBC 4.8 million Hgb 12.4 Gm WBC 9700 Differential polymorphonuclears 84%, lymphocytes 12.5% and monocytes 3.5% Total eosinophilic count zero Resistometer normal Platelets normal Glucose tolerance test fasting 121 mg % $\frac{1}{2}$ hr 263 mg %, 2 hrs 320 mg % 3 hrs 182 mg % Urine sugar 4% at 3 hrs 17 ketosteroids 17.5 mg/24 hrs *Roentgenographic findings* Normal skull pelvis and pyelograms *Treatment* Roentgen therapy—4 000 r over 2 portals (skin dose)

PROGRESS BY MONTHS

- 2 Testosterone 10 to 50 mg 3 times a week Adrenal exploration Right adrenal slightly increased in size 70% resected Left adrenal 90% resected
- 4 Slight general improvement 1/ ketosteroids 36 mg/24 hrs
- 6 No improvement Differential polymorphonuclears 59% lymphocytes 19.5% monocytes 11% and band forms 6.5% Total eosinophilic count zero
- 7 Rotational roentgen therapy 4 500 r (tumor dose)
- 9 Less hunger Questionable improvement
- 11 Improvement began shortly after last visit Muscular weakness is less severe No further ecchymoses Edema is not evident Swelling of face subsiding Hair growth becoming blacker BP 180/100 Differential polymorphonuclears 63% lymphocytes 32% monocytes 32% and eosinophils 1% Serum potassium 21.2 mg % Serum sodium 47.8 mEq/l
- 13 133 lbs BP 160/100 Rounded faces gone No edema
- 14 Weakness of legs slight No excess hair on face BP 170/100 Glucose tolerance test fasting 87 mg % $\frac{1}{2}$ hr 141 mg % 2 hrs 131 mg % 3 hrs 125 mg % No glycosuria Total eosinophilic count 92/cu mm

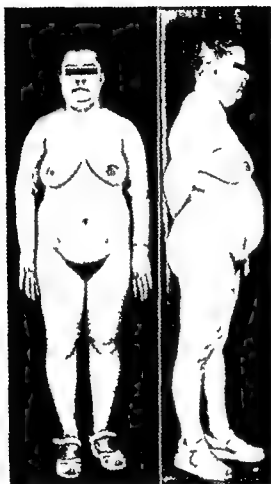


FIG 102 CUSHING'S SYNDROME (See Protocol 11 XXIV) Re-establishment of menstruation and loss of weight without dieting after roentgen therapy

SECTION 12

CHROMOPHOBE TUMORS

(Analysis of 144 cases presumed or verified¹)

I PHYSICAL STATUS

		PER CENT
A SEX		
1 Males	73	
2 Females	71	
III AGE—Onset (approximate)		
	PER CENT	
1 13 to 19	11	
2 20 to 29	20	
3 30 to 59	60	
4 60 and over	9	
C WEIGHT		
1 Normal, no change	43	
2 Under	26	
3 Over	30	
D VISUAL CHANGES		
1 Optic atrophy (unilateral or bilateral)		81
2 Field defects		82
3 Acuity absent or reduced, one or both eyes		76.7
F AXILLARY AND PUBIC HAIR		
1 Normal		18
2 Decreased or absent		72
F BLOOD PRESSURE		
1 Range	80/50 to 230/100	
2 Average	118/72	
3 Systolic		
		PER CENT
a Below 120		39
b Below 100		8
c Above 145		13

II SYMPTOMATOLOGY

A SEXUAL LIBIDO		
1 Absent or decreased (50% under 40 years of age)		72 per cent of those questioned
2 Increased		Less than 1 per cent (1 case)
B AMENORRHEA (before age of 42)		57 per cent
C MISCELLANEOUS		CASES PER CENT
1 Visual changes (as a complaint)		80
a Blurred	74	
b Halved vision	29	
c Blind one eye	12	
d Blind, both eyes	2	
e Diplopia	15	
f Unilateral ptosis	3	
g Strabismus	1	
h Scotoma	2	
2 Headaches		21
3 Fatigability		14
4 Drowsiness		7.1
5 Pallor		7
6 Polydipsia less than		1 (1 case)
7 Numerous other complaints		

III LABORATORY DATA

A RED BLOOD CELLS		
1 Range (all cases)	3.4 to 5.5 million	
2 Average	4.4 million	

B HEMOGLOBIN		
1 Range (all cases)		68 to 104 per cent
2 Average		85 per cent
C BLOOD SUGAR (fasting)		
1 Range (49 cases)		73 to 137 mg %
2 Average		84.9 mg %
D PLASMA CHOLESTEROL		
1 Range (74 cases)		133 to 398 mg %
3 cases		Over 250 mg %
2 Average		230 mg %
E BASAL METABOLIC RATE		
1 Range (86 cases)		Plus 5 to minus 40 per cent
2 cases		Above minus 10 per cent
2 Average		Minus 20 per cent

TABLE 9 RESULTS OF TREATMENT OF 144 CASES OF CHROMOPHOBE TUMOR¹

NO OF CASES	VISION BEFORE TREATMENT	SURGICAL AND ROENTGEN THERAPY		ROENTGEN THERAPY ONLY	HORMONAL THERAPY (ONLY)*	VISION AFTER TREATMENT	RESULTS OF TREATMENT
35	Treatment because of other symptoms rather than eye changes	1	12	12	9	Normal	Improved Unchanged Worse
16	Incapacitated by loss of sight	7	5	4		Very good	Marked improvement post operatively able to resume normal occupation
41	Impaired but patient still at work	8	20	13		Good	Improved after operation able to continue normal occupation
15	Incapacitated by loss of sight	5	9	1		Moderate	Slight operative improvement sufficient only for intermittent work or new occupation
9	Impaired but patient still at work	2	4	3		Satisfactory	No change after operation continued with normal occupation
3	Incapacitated by loss of sight	2	1			Poor	No change after operation no useful vision remained for work or reading
5	Various degrees of impairment	2	2	1		Progressive deterioration	Failing vision or other disabling symptoms continued to progress or new complaints developed within 6 months
3							No follow up
17	Various degrees of impairment	10	6	1			Postoperative deaths and one during roentgen therapy
144	Total	36	49	47	9		

* Hormonal therapy used when indicated

IV THERAPEUTIC RESULTS

A SUMMARY

1 Follow up of 26 cases after 10 years or more¹

a Treatment	CASES
(1) Operation	23
Postoperative deaths	3
(2) Roentgen radiation	2
(3) None	1
b Vision	
(1) Normal or improved	19
(2) Worse	2
(3) Blind	2

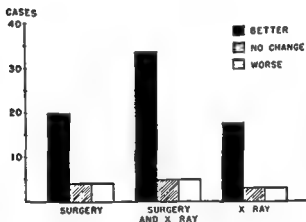
2 Follow up of 124 cases (of 144¹, Chart 26 and Table 9) for 1 to 25 years

a Treatment	CASES
(1) Operation (including secondary operations)	36
Postoperative deaths	16
(2) Operation and roentgen radiation	49
(3) Roentgen radiation (1 death)	47
(4) Hormonal	9
b Vision—see Table 9 and Chart 26	

REFERENCE

- 1 Horrax G H Hare H F, Younghusband O and Hurthall L M Unpublished data

RESULT OF TREATMENT ON VISION



RESULT OF TREATMENT IN PATIENTS WITHOUT VISUAL CHANGE

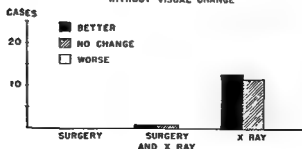


CHART 26 SUMMARY OF THERAPEUTIC RESULTS IN PATIENTS WITH CHROMOPHOBE TUMOR (presumed or verified) (Younghusband O Hurthall L M Horrax G H and Hare H F Unpublished data)

SECTION 13

SUMMARY ON PITUITARY TUMORS

I TUMORS IN THE REGION OF THE SELLA

- A ADENOMA
- B CRANIOPHARYNGIOMA
- C SUPRASellar MENINGIOMA
- D ANEURYSM
- E GLIOMA OF THE OPTIC CHIASMA
- F CHOLESTEATOMA
- G ASTROCYTOMA
- H CHORDOMA

II INCIDENCE

	PER CENT
A ADENOMA	28 (of all intra cranial tumors)
1 Chromophobe	70
2 Chromophil	19.4
3 Mixed	10.6
B CRANIOPHARYNGIOMA	4.5 (of all intra cranial tumors)
C ALL OTHERS LESS THAN	1.0

III AGE¹

- A ADENOMAS
 - 1 Range—15 to 65 years
 - 2 Peak at 35 years
- B CRANIOPHARYNGIOMA
 - 1 Range—2 to 63 years
 - 2 Peak around 15 years

IV DIFFERENTIATION OF ADENOMAS FROM OTHER SELLAR TUMORS^{10 11}

- A MENINGIOMA
 - 1 Adults usually
 - 2 Glandular signs and symptoms are not marked
 - 3 Sella
 - a Normal
 - b Deformed slightly with some evidence of proliferation at the tuber culum sellae

- 4 Visual fields
 - a Optic atrophy
 - b Bitemporal field defects are often much more advanced in one eye
- 5 Ventriculography—see 2 VIII F 6
- B CRANIOPHARYNGIOMA (see 3 IV)
 - 1 Most frequent in children but do occur in adults
 - 2 Sella
 - a Calcification above it in 70 to 80 per cent
 - b Enlarged
 - c Deformed
 - d Not symmetrically ballooned
 - 3 Tumor often protrudes posteriorly behind the chiasma into the third ventricle producing hydrocephalus
 - 4 Choked disks sometimes instead of optic atrophy
 - 5 Ventriculography—see 2 VIII F 6
- C ANEURYSM (see Fig 104)
 - 1 Glandular symptoms are lacking in most cases (see Protocol 7 VII)
 - 2 Sella
 - a Enlarged as in adenomas
 - b Deformed
 - c Sharpening or elevation of one anterior clinoid
 - d Characteristic crescentic shadow may be present on the roentgenogram
 - 3 Visual fields have a tendency to be temporal defects
 - a Homonymous
 - b Incomplete
 - 4 Arteriograms (roentgenograms taken during injection of thorotrast into the common carotid) give positive diagnosis (see 2 VIII F 5)
- D RARE TUMORS (gliomas of the optic chiasm or nerves, cholesteatomas and others)
 - 1 Glandular manifestations are not present usually
 - 2 Sellar expansion is not seen as in adenomas
 - 3 Visual fields
 - a Bizarre
 - b Hemianopsias (not clear-cut)

V MIXED TYPES (see Figs 103, 105 and 106)

A CLINICAL MANIFESTATIONS

- 1 *Hyperpituitarism to hypopituitarism—beginning with signs of chromophil tumor (hyperpituitarism) and ending with findings of a chromophobe tumor (hypopituitarism)*
- 2 *Hypopituitarism to hyperpituitarism*
 - a Onset with signs of chromophobe tumor and terminating with findings of a chromophil type
 - b Dwarfism to gigantism
- 3 *Simultaneous hyperpituitarism and hypopituitarism*
 - a Tumor may be initially composed of both chromophils and chromophobes with variations in basophilic cells
 - b This may be the reason in some cases for conflicting evidence as regards the establishment of hypopituitarism and hyperpituitarism
 - c Hypopituitarism may accompany¹
 - (1) Urinary gonadotropins in excess
 - (2) Hot flashes in menopausal women
 - d Growing pituitary giants with hypersecretion of growth hormone may also have hypopituitarism

VI SYMPTOMATOLOGY

A TUMOR EXPANSION (see Fig 24 p 109)

- 1 Headache
 - a Acromegaly particularly
 - b Location
 - (1) Frontal
 - (2) Bitemporal
 - c Vague
 - d Persistent
- 2 Visual changes
 - a Chromophobe type especially
 - b Fields restricted
 - c Hemianopsia
 - (1) Unilateral
 - (2) Bilateral
- 3 Drowsiness
- 4 Polydipsia
- 5 Unicentric attacks
- 6 Mental effects
 - a Aberrations
 - b Confusion
 - c Depression psychosis

7 Lacrimation—absent (rare)⁹

8 Gait may be affected

B FROM DEFICIENT PITUITARY SECRETION

- 1 Before puberty
 - a Growth retarded
 - b Sexual development delayed
 - c Mentally alert, except when tumor
 - d Pallor
 - e Anemia
- 2 After puberty
 - a Libido decreased
 - b Amenorrhea
 - c Hair decreases
 - d Weight gain (see Fig 103)
 - e Pallor in some
 - f Fatigue
 - g Lethargy
 - h Somnolence
- 3 Simmonds' disease (complaints as in anorexia nervosa)
 - a Vomiting
 - b Weight loss
 - c Emaciation
 - d Amenorrhea
- 4 Thyroid deficiency (symptoms like myxedema)
 - a Drowsiness
 - b Coldness
 - c Skin—dry
 - d Pulse—slow
 - e Patient may also have adrenal symptoms
- 5 Adrenal insufficiency (symptoms like in Addison's disease)
 - a Weakness
 - b Weight loss
 - c Anorexia
 - d Hypoglycemic attacks
- 6 General (signs or symptoms related to hypopituitarism not mentioned elsewhere)
 - a Beard scant
 - b Hair texture changes
 - c Weight gain

C FROM EXCESS PITUITARY SECRETION

- 1 Increase in
 - a Height
 - b Acral parts
- 2 Menses
 - a Amenorrhea
 - b Oligomenorrhea
- 3 General (signs and symptoms related

to pituitary disease with acromegaly or gigantism not listed elsewhere)

- a Hypertrichosis
- b Pigmentation
- c Skin fibromata
- d Asthenia
- e Parasthesias
- f Blood pressure is low
- g Lactation persists
- h Libido decreased
- i Spontaneous rupture of tumor
- j Sexual characteristics may return without treatment

VII SURGICAL TREATMENT

A OPERATIONS FOR PITUITARY TUMORS OR CYSTS^{1 5 7 10 11}

1 Transfrontal approach (see Figs 107-110)

- a A relatively small osteoplastic bone flap just above the right frontal sinus is used to avoid danger of infection from the latter (usually easier for right handed surgeon)
- b The scalp incision, almost wholly within the hairline is
 - (1) Curvilinear
 - (2) Reflected forward
- The dura ■ retracted from the inner surface of the skull and orbital plate down to the sphenoidal ridge where it is attached
- d The dural incision is carried forward and upward over the tip of the frontal lobe for maximum retraction with the least possible injury
- e An abundance of fluid is practically always obtained by a slight nick into the subarachnoid space
 - (1) It ■ usually unnecessary to tap the lateral ventricle
 - (2) A ventricular needle may be inserted perpendicularly through the lateral posterior portion of the field
- f A smooth flat spatula or lighted retractor is now used to draw back the frontal lobe which is protected over its upper portion by the dura
- g The upper surface of the adenoma is immediately recognized protruding

just medial to the right optic nerve in the space between the chiasm and the tuberculum sellae

- h The nerve and the surface of growth are covered by the arachnoid which must be carefully incised to allow further retraction of the frontal lobe back to the chiasm and medially to the left optic nerve
- i The nerves may be so widened and flattened by compression that they can scarcely be distinguished from the actual surface of growth
- j A needle attached to a syringe is inserted into the tumor for two purposes to

(1) Withdraw cystic contents if present

(2) Determine if an aneurysm is there (withdrawal of fresh arterial blood would establish the fact)

(a) The needle is removed if an aneurysm is found

(b) Entrance point of needle is sealed by

[1] A piece of muscle from the temporal region held securely in position there

[2] Gelfoam

2 Transphenoidal approach⁶

- a Indication—tumors not accessible by transfrontal route
- b This method ■
 - (1) Used rarely
 - (2) Not recommended except in the hands of those who are accustomed to this operation

3 Procedures for specific types

- a Solid adenoma
 - (1) Circular opening ■ made in the capsule
 - (2) Soft reddish gray tissue is spooned or sucked out as completely as possible
 - (3) Capsule ■ gently separated and pulled away from the optic nerves and chiasm
 - (4) Portion lying above the sella turcica is
 - (a) Excised

(b) Shriveled by electrocoagulation

b Cystic adenoma

- (1) Large incision made in capsule
- (2) Liquid contents removed
- (3) Solid portion excavated by
 - (a) Long pituitary scoops
 - (b) Strong suction

■ Chromophobe tumors sometimes cause internal hydrocephalus by their growth upward and back of the chiasm into the region of the third ventricle

- (1) These are the most dangerous and difficult surgical tumors
- (2) Operative mortality varies from 3 to 5 per cent (30 to 40% reported in the literature)
- (3) It may be necessary to
 - (a) Sacrifice one optic nerve
 - (b) Resect a portion of the frontal lobe

d Extensive growth behind and above one chiasm or any extension under either temporal lobe (see Fig 111 and 112)

- (1) Capsule may be
 - (a) Grasped by alligator forceps and drawn forward
 - (b) Excised above the sella in smaller tumors
 - (c) Left undisturbed at intrasellar portion with flattened pituitary body below it
- (2) Tumor must be evacuated completely as possible with
 - (a) Suction
 - (b) Scooping
- (3) Portion of cortex (temporal) may be
 - (a) Excised partially
 - (b) Transected

4 Comment

a Pituitary adenomas

- (1) Solid usually
- (2) Contents are variable
 - (a) Extremely soft
 - (b) Degenerated material
 - (c) Firm fibrous growth (difficult to remove)

■ Complete evacuation of adenomas should be attempted

- (1) This may be hazardous

(2) Great care must be taken in freeing the tumor when it extends laterally into the region of the carotid arteries

B RESULTS—see 12 IV and 13 VIII

VIII PREOPERATIVE AND POST OPERATIVE MANAGEMENT

A EVALUATION OF PATIENT'S CONDITION

- 1 Preoperative severity is greater if
 - a Patient is cachectic
 - b Clinical myxedema is present
 - c Tumor is extensive
 - d Intracranial pressure is increased
 - e Anemia is severe
 - f Water test is positive
 - g Basal metabolic rate is low
 - h 17 ketosteroids are decreased
- 2 Postoperative prognosis is worse with
 - a Extensive pituitary extirpation
 - b Intracranial complications as
 - (1) Localized hemorrhage
 - (2) Edema of brain
 - c Infection
 - (1) Intracranial
 - (2) Elsewhere
 - d Hyperthermia
 - e Acute adrenal insufficiency
 - f Potassium loss, when marked
 - g Elevation of (possible delayed alarm reaction)
 - (1) Nonprotein nitrogen
 - (2) Sodium
 - (3) Chlorides

B PREOPERATIVE CARE WHEN HYPOPITUITARISM IS PRESENT

- 1 Desoxy corticosterone
 - a Indication—for severe adrenal insufficiency if ACTH or cortisone used not needed
 - b Dosage—parenteral 5 mg daily, 3 to 4 days before operation
- 2 Adrenocorticotrophic hormone or cortisone
 - a Indication—when moderate or severe hypofunction exists—given 3 to 4 days before and after operation
 - b Dosage
 - (1) Cortisone—25 to 50 mg/day
 - (2) ACTH—40 mg/day or effective dose see 106 III E
- 3 Testosterone propionate
 - a Indication—marked malnutrition

- b Dosage—intramuscular, 25 mg daily for 4 to 5 days (or longer) before surgery
- 4 Protein equivalent to 10 Gm of nitrogen
 - a Dosage
 - (1) Orally
 - (2) Hydrolysates
 - b Result—extent of utilization is questionable
- 5 Salt—dosage
 - a Oral—5 to 10 Gm
 - b Intravenous—1,000 to 2,000 cc daily
- 6 Potassium salts
 - Indication—to adjust electrolyte balance, rarely required
 - b Dosage
 - (1) Oral (citrate 20% solution)—4 to 8 cc in fruit juice daily
 - (2) Intravenous (chloride)—3 to 4 Gm with intravenous fluids daily

C POSTOPERATIVE COMPLICATIONS

- 1 Intracranial complications
 - a Surgical measures may be necessary
 - b Lumbar puncture for increased spinal fluid pressure
- 2 Hyperthermia
 - a Penicillin
 - b Cold packs
- 3 Acute adrenal insufficiency—dosage of medications
 - a Adrenocorticotrophic hormone—intramuscular 25 to 200 mg daily
 - b Cortisone—oral or intramuscular, 50 to 100 mg daily
 - c Adrenocortical hormone (aqueous)—subcutaneous 10 to 30 cc daily, gradually reduce
 - d Desoxycorticosterone—parenteral 5 mg daily
 - e Glucose—intravenous, 5 per cent solution in saline 2,000 cc daily
- 4 Potassium deficiency—see above—B 7
- 5 Sodium retention
 - a Ammonium chloride—oral 15 gr qid
 - Glucose intravenously
- 6 Diabetes insipidus—may be transient (see 8 XVI)

IX ROENTGEN THERAPY⁶

A TECHNIC

- 1 Factors
 - a K V P 200
 - b Distance 50 or 70 cm
 - c Filter 1 mm copper and 1 mm aluminum
 - d Ma 20
 - e Portals 5 cm—temporal directing beam at sella turcica
- 2 Dosage (r = roentgen units)
 - 1 Daily dose
 - (1) 300 to 400 r (measured in air)
 - (2) Give 1 treatment daily
 - (3) Alternate parts every other day
 - b Total dose
 - (1) First series—8 to 12 treatments
 - (2) 1 200 to 1,800 r to each portal
 - c Tumor dose—1 200 to 1,800 r approximately
- 3 Treatment—may be repeated every 2 months depending on indications
- 4 Rotational therapy permits larger doses to be given without skin damage (method by Hare and Trump⁷)
 - a Dose—up to 4 500 r in 18 days
 - b Method of choice in
 - (1) Active acromegaly
 - (2) Cushing's syndrome without adrenal tumor

B COMPLICATIONS

- 1 Immediate
 - a Development after 1 200 r or more in 300 to 400 r daily
 - b Radiation sickness denoted by
 - (1) Nausea
 - (2) Vomiting
 - (3) Severe headache from edema occasionally
 - c Symptoms disappear within 48 hrs
- 2 Intermediate
 - a Development—3 weeks following above radiation therapy
 - b Hair
 - (1) Depilation in treated area
 - (2) Regrowth may take place in approximately 2 months time
 - c Skin may show variable degrees of erythema to blistering

- d Tumor alterations
 - (1) Two common changes are
 - (a) Edema
 - (b) Hemorrhage
 - (2) Temporary increased pressure on optic nerves may occur from these two complications
 - (3) Check by frequent visual field examinations
- 3 Delayed
 - Develop after repeated series of roentgen radiation as much as 3,000 to 4,000 r to each skin area
- b The following may occur
 - (1) Atrophy of the
 - (a) Muscles
 - (b) Subcutaneous tissue
 - (c) Skin (with telangiectasia)
 - (d) Bones
 - (2) Brain fibrosis
 - (3) Depilation permanently

REFERENCES

- 1 Bailey P Intracranial Tumors ed 2 Springfield Ill Thomas 1933 p 136
- 2 Cushing H Intracranial tumors in Osler's Modern Medicine Philadelphia Lea & Febiger Vol 6 1928 pp 222 254
- 3 — Intracranial Tumors Springfield Ill and Baltimore Md Thomas 1932
- 4 Dott N M Bailey I and Cushing H A consideration of the hypophysial adenomata Brit J Surg 13 314 366 (Aug) 1925
- 5 Grant F Surgical experience with pituitary tumors (adenomas and craniopharyngiomas) JAMA 136 668 672 (Mar) 1948
- 6 Hare H F Personal communication
- 7 Henderson W R Sexual dysfunction in adenomas of pituitary body Endocrinology 15 111 127 (Mar Apr) 1931
- 8 Hirsch O Die operative Behandlung von Hypophysistumoren nach endonasalen Methoden Arch f Laryngol u Rhinol 26 529 686 1912
- 9 — Surgery's contribution to our knowledge of pituitary function Confans neurol 7 45 54 (Jan) 1946
- 10 Horrax G H The Pituitary Gland Baltimore Williams & Wilkins 1938 pp 665 682
- 11 — Personal communication
- 12 Horrax G H Hare H F Youngshu Band O and Hurxthal L M Unpublished data
- 13 Poppen J L Ventricular drainage as a valuable procedure in neurosurgery report of satisfactory method Arch Neurol & Psychiat 30 587 589 (Nov) 1943

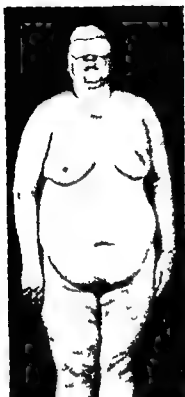


FIG 104 ANEURYSM OF RIGHT INTERNAL CAROTID Age 54 female Right optic atrophy was caused by this aneurysm Verified by operation The above roentgenogram was taken several years later after a thorotrast injection of the right common carotid artery Sella was not enlarged

FIG 103 HYPOPITUITARISM—MIXED TUMOR (verified) Age 32 Chief complaints Failing vision 6 months amenorrhea and gain of 100 lbs in years Findings Skin smooth and pale Normal hair distribution Bilateral hemianopsia Plasma cholesterol 219 mg % BMR minus 30% FSH negative (twice) Sella enlarged with erosion into sphenoid sinus on left Microscopic diagnosis first operation predominantly chromophil growth Recurrence 18 months later unchanged by roentgen therapy Reoperation chromophobe tumor No restoration of vision



FIG 105 PANHYPOTUITARISM—MIXED PITUITARY ADENOMA (verified) (Postoperative photograph) Age 26 Failing vision bitemporal headache loss of libido no beard Regression of secondary sex characteristics Note smooth feminine facial features Plasma cholesterol 116 to 136 mg % BMR minus 18% Craniotomy with restoration of vision and return of normal hormonal secretions

FIG 106 SKULL IN MIXED PITUITARY TUMOR
 Age 23 female Excessive perspiration enlargement of hands and feet also coarsening of facies Headache amenorrhea and blurred vision with bitemporal hemianopsia Hair normal No anemia BMR plus 15% Operation because of sudden increase in visual disturbance No preoperative roentgen therapy given Pathologic report adenoma of mixed chromophobe and eosinophilic type Note large sella and comparatively little bony change in skull



FIG 107 SURGICAL TREATMENT OF PITUITARY TUMORS Transfrontal craniotomy illustrating coronal incision entirely within hair line (a) Forward reflection of skin bone flap turned down over right frontal area (b) Retraction of dura over right frontal lobe and line of incision in dura along sphenoidal ridge (Horrax G. The Pituitary Gland Baltimore Williams & Wilkins pp 665 682)

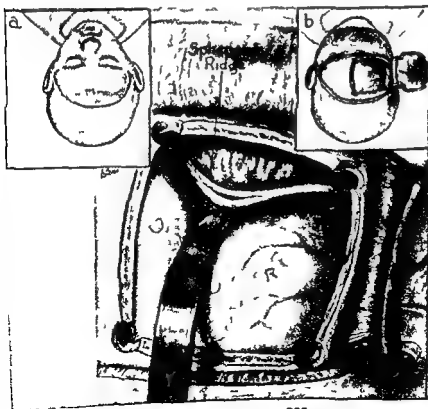




FIG 108 SURGICAL TREATMENT OF PITUITARY TUMORS Steps in the removal of a pituitary adenoma. The large upper sketch shows the frontal lobe retracted after dura has been incised, right optic nerve exposed and adenoma protruding medial to nerve. (A) shows beginning removal of adenoma by scoop after incision into capsule. Insert (B) illustrates wider opening of capsule and further evacuation of contents by suction. Insert (C) shows removal of upper portion of capsule after it has been with drawn from under the optic nerves and chiasm. (Horrax G. *The Pituitary Gland*. Baltimore: Williams & Wilkins, pp. 665-682.)

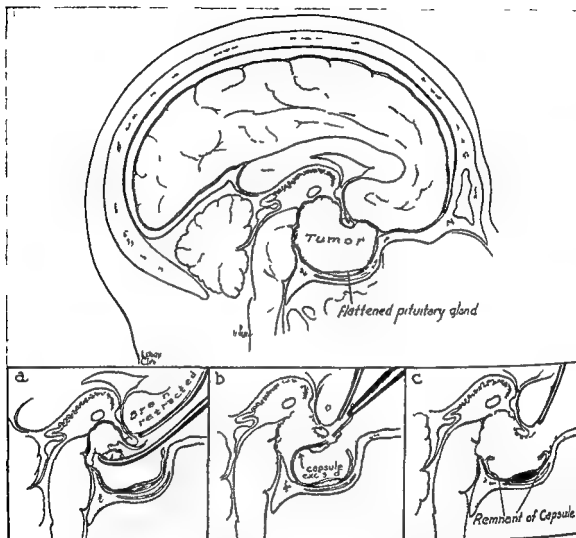


FIG 109 SURGICAL TREATMENT OF PITUITARY TUMORS Removal of large adenomas which have extended backward and upward behind the chiasm. Large upper diagrammatic sketch shows the relative size and situation of the tumor extending upward into the third ventricle and backward to compress the pons. Inserts (a) (b) and (c) illustrate the successive steps in removing the tumor contents withdrawal and partial excision of capsule (Horrax G. *The Pituitary Gland* Baltimore: Williams & Wilkins pp 665-682)

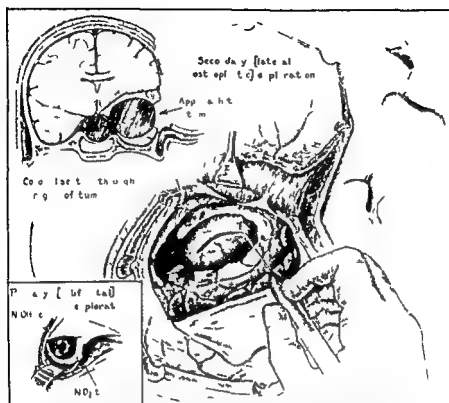


FIG 110 SURGICAL TREATMENT OF PITUITARY TUMORS Method of removing a large temporal extension of pituitary adenoma by a secondary (temporal) bone flap (Cushing H Intracranial Tumors Thomas Springfield Ill p 17)

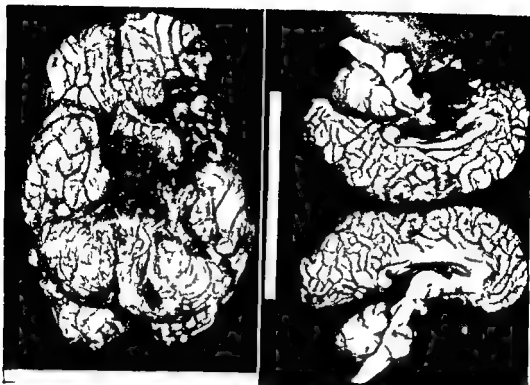


FIG 111 PITUITARY ADENOMA WITH LEFT TEMPORAL EXTENSION Patient was operated upon by Dr Harvey Cushing in 1930 for a large pituitary adenoma with an extension into left temporal lobe. He remained well for approximately 8 years. *Chief complaints* Decreased vision anosmia weakness of right side of body aphasia and mental deficiency lethargy and somnolence. *Examination* Marked hypopituitary signs bilateral primary optic atrophy right lower facial weakness and overactive deep reflexes on right. Blood count and urine normal. Blood sugar 70 mg % Plasma cholesterol 2.5 mg % BMR minus 34%. Patient had second operation in 1938 left temporoparietal craniotomy with extensive capsular and intra capsular removal of huge recurrent pituitary adenoma.



FIG 112 PITUITARY ACIDOPHILIC ADENOMA A very large symptomless extension of a pituitary acidophilic adenoma into the right temporal lobe. Homonymous hemianopsia was not found in spite of the size of the metastatic lesion (Cushing H and Davidoff L M The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance Monograph Rockefeller Institute for Medical Research No 22 p 73)

CHAPTER 3

Thyroid

PRECLINICAL

Section 14 PRELIMINARY

- I HISTORY
- II ANATOMY
- III EMBRYOLOGY
- IV CONGENITAL ANOMALIES
- V HISTOLOGY
- VI FUNCTIONS
- VII CHEMISTRY
- VIII BIO ASSAY
- IX PATHOLOGY
- X CLASSIFICATIONS
- XI and XII CHIEF CLINICAL FINDINGS OF HYPOSECRETION
AND HYPERSECRETION
- XIII EXAMINATION OF PATIENT

CLINICAL

Section

- 15 ENDEMIC GOITER
 - 16 COLLOID GOITER
 - 17 NODULAR (MULTIPLE) GOITER
 - 18 INTRATHORACIC GOITER
 - 19 THYROIDITIS—ACUTE NONSUPPURATIVE AND
SUPPURATIVE
 - 20 CHRONIC NONSPECIFIC THYROIDITIS
 - 21 REIDEL'S STRUMA
 - 22 HASHIMOTO'S STRUMA
 - 23 INFECTIOUS GRANULOMATA
 - 24 CRETINISM
 - 25 MYXEDEMA
 - 26 HYPERTHYROIDISM
 - 27 PERSISTENT HYPERTHYROIDISM
 - 28 RECURRENT HYPERTHYROIDISM
 - 29 APATHETIC HYPERTHYROIDISM
 - 30 THE THYROCARDIAC PATIENT
 - 31 HYPERTHYROIDISM AND DIABETES MELLITUS
 - 32 HYPERTHYROIDISM AND PREGNANCY
 - 33 EXOPHTHALMIC SYNDROME
 - 34 FACTITIOUS HYPERTHYROIDISM
 - 35 TUMORS
-

PRELIMINARY SECTION 14

I HISTORY

About 700 B C

A.D. 23-79 Plinius¹¹⁴

A.D. 130-200 Galen⁴
600

c. 630 Iulus Aegineta¹¹¹

1170 Ἰωάννης of Salerno¹

1543 Vesalius¹⁴¹

1562 Revidus Columbus³

1563 Gallopio³⁵

Early part
seventeenth
century Paracelsus¹⁰⁰

1629 May¹⁰⁴

1656 Wharton¹⁰

1657 Hofer⁹⁷

1722 de Saint Yves²

1749 Haller³⁰

1769 Prosser¹¹⁶

1786 Larry¹¹⁰

1800 Lodré⁴⁰

1800 Hedenus⁶

1800 Pinsuti¹¹³

1802 Flajani³⁹

1806 Meckel¹⁰⁸

1811 Burns¹⁷

1813 Blizard¹⁴

1813 Courtois⁷

1820 Coindet[—]

1830 Langl¹⁵

1832 Cooper¹

1834 Prout¹¹⁷

1835 Graves⁴⁵

1835 N. R. Smith¹³²

Assyrian bas reliefs probably showed a case of exophthalmic goiter, medical scripts from ancient Egypt and Rome recognized the occurrence of goiter as due to some factor in water ingested; operative treatment mentioned, sculptures showed signs of goiter and exophthalmos.

Impure water said to be the cause of goiter.

Thyroid produces a lubricating fluid for the larynx.

Chinese treated cretinism with sheep thyroid glands.

Resection of goiter attempted.

Seaweed and sponges were used for treatment of goiter; surgery performed if these failed.

Thyroid gland described for the first time.

Thyroid gland weight stated to be a little over one ounce larger at birth and in females.

Congenital goiter recorded.

Relationship between cretinism and endemic goiter established.

Ligation of afferent arteries to thyroid.

Thyroid gland given its name.

Goiter may be produced by air, water and food.

Three patients with exophthalmos and goiter were reported.

Intrathoracic goiter noted.

First recorded use of an iodine preparation for the cure of goiter in England.

Classical account of exophthalmic goiter.

Cretinism considered to be due to concentrated air in deep valleys rather than to water; skeletal changes recognized.

Six successful operations for goiter.

Thyroid juice suggested as a therapeutic measure.

Exophthalmic goiter described and related cardiac disturbances noted.

Puberty and pregnancy cause an increase in size of the thyroid gland.

Carcinoma of thyroid reported.

Ligation of superior thyroid artery in treatment of toxic goiter.

Iodine obtained from seaweed.

Iodine used in treatment of thyroid disorders.

Intrathoracic goiter recognized clinically.

Enlarged thymus noted at postmortem in a case of Graves's disease.

Reports published on giving iodine compound in treatment of goiter (actually first used as a remedy for goiter in 1816).

Exophthalmic goiter described.

First operation for goiter in America.

1836	Cooper	Thyroidectomy in animals produced peculiar symptoms
1836	King ⁷	Endocrine function of thyroid gland suggested
1840	von Bräsdow ¹⁴²	Exophthalmic goiter discussed, iodine given to two patients with excellent results, exophthalmos due to increased connective tissue
1849	Begbie ¹¹	Exophthalmos was caused by increased vitreous humor
1849	Dalrymple ³⁰	Special eye sign demonstrated in exophthalmic goiter
1850	Curling ⁷⁹	Clinical picture of cretinism noted, and thyroid deficiency suggested as the reason
1851	Niépce ¹⁰⁰	Pituitary enlargement in cretins
1853	Demarres ³¹	Exophthalmos was the result of excessive fat in ocular tissues
1858	von Müller ¹⁴⁸	Spasm of smooth muscle fibers caused exophthalmos
1859	Schiff ¹⁷⁷	Fatal results of thyroidectomy preventable by intra abdominal transplantation of the gland
1863	Trousseau ¹³⁶	Effective trial of iodine in treatment of Graves's disease occurred by error
1864	von Graefe ¹⁴⁴	Diagnostic eye sign of exophthalmic goiter described
1867	Sick ¹³¹	First total extirpation of the thyroid in a child with a description of postoperative myxedema
1869	Cheadle ¹⁹	Transitory and favorable effect from iodine administration in exophthalmic goiter
1869	Stellwag ¹³⁵	Special eye sign noted in hyperthyroidism
1871	Fagge ³⁷	Cretinism due to absence or atrophy of the thyroid
1874	Gull ¹⁸	Cause of myxedema established
1874	Watson ¹⁴⁹	Partial thyroidectomies performed for treatment of toxic goiter
1876	Runge, ¹⁻⁴ Cohnheim ¹	Metastatic thyroid growths without obvious carcinoma in that gland were observed
1877	Baber ⁷	Extensive histologic studies on the thyroid gland of many animals
1878	Kocher ⁷⁰	Thyroidectomies for hyperthyroidism performed more successfully
1878	Ord ¹⁰⁷	The term 'myxedema' was coined
1882	Reverdin ¹¹⁹	Myxedema produced in humans by partial or total removal of thyroid
1883	Kocher ⁷⁷	Myxedema following thyroidectomy was termed 'cachexia strumipriva'
1883	Marie ⁹⁰	Tremor was recognized as a sign of exophthalmic goiter
1883	Mobius ⁹⁹	Special eye sign demonstrated in hyperthyroidism
1883	Wolfier ¹³³	Classification of thyroid tumors
1884	Horsley ⁶⁸	Total removal of thyroid in a monkey induced myxedema (parathyroids were also extirpated)
1884	Rehn ¹¹⁸	Excess thyroid secretion caused Graves's disease
1885	His ⁶⁶	Double origin of human thyroid noted in embryos
1887	Savill ¹⁻⁵	Myxedema common to both sexes
1888	Bernays ¹	Sublingual thyroid described
1888	Rogowitsch ¹⁻³	Thyroidectomy in rabbits resulted in pituitary hypertrophy
1890	Bettencourt and Serrano ¹³	Thyroid grafts produced temporary relief of myxedema

1890	Lannelongue ⁸⁷	Thyroid transplantation for treatment of cretinism
1890	Vassale ¹³⁵	Thyroid extracts given to experimental thyroidectomized animals with improvement
1891	Murray ¹⁰⁹	A glycerin extract of a sheep's thyroid was injected hypodermically for treatment of myxedema with satisfactory results
1892	Mackenzie ⁸⁷ and Fox ⁴¹ (independently)	Myxedema treated with success by oral administration of dried thyroid gland
1893	Bruns ¹⁷	Caseous tuberculosis may develop in thyroid gland
1893	Greenfield ¹⁶	Thyroid hyperplasia caused increased functional activity in Graves's disease
1893	Joffroy ⁷⁷	Special eye sign reported in hyperthyroidism
1893	Müller ¹⁹¹	Increased basal rate and altered protein metabolism were discovered in exophthalmic goiter cases
1894	Beclère ¹⁰	Induced hyperthyroidism recognized
1895	Ballet and Enriquez ⁹	Serum of myxedematous patients tried in treatment of toxic goiter
1895	Baumann ⁹	Thyroid contains iodine an iodine-containing compound (thyroiodin) isolated
1895	Magnus Levy ¹⁰	Work of Müller confirmed and the foundation laid for the concept of thyroid function
1895	von Mikulicz ¹⁴⁷	First operation for relapse of exophthalmic goiter
1896	Riedel ¹²⁰	Chronic inflammation of thyroid described
1896	Vassale and Generali ¹¹⁰	Myxedema produced by thyroidectomy and removal of parathyroids caused tetania thyreopriva
1897	Brissaud ¹⁸	Thyroid infantilism demonstrated
1899	Oswald ¹⁰⁸	Thyroglobulin isolated from thyroid gland
1899	Schiff ¹⁹⁰	Substernal goiter illustrated by roentgenograms
1902	Primeau ¹²	Endemic (familial) cretinism with goiter observed
1903	Williams ¹	Roentgen therapy for toxic goiter
1904	MacCallum and Cornell ⁹⁸	Cervical sympathetic stimulation resulted in exophthalmos
1905	Abbe ¹	Radium inserted into thyroid for treatment of Graves's disease
1905	von Hansemann ¹⁴⁶	Enlarged thymus was cause of Graves's disease
1905	Hunt ⁷⁰	Acetonitril test showed that activity of thyroid preparations are proportional to their iodine content
1906	Gifford ⁴⁷	Special eye sign in exophthalmic goiter
1906	Schrager ¹³⁹	The term 'lateral aberrant thyroid' suggested
1907	Kocher ⁷³	First to stress treatment with iodine in exophthalmic goiter also advised removal of one lobe and isthmus with ligature of one thyroid artery on opposite side
1907	Ungermann ¹⁵³	Lingual thyroid discovered
1908	Hunt and Seidell ⁷¹	Pertinency of iodine to physiologic activity of thyroid preparations was proven
1908	Kocher ⁷³	Lymphocytosis in toxic goiter recognized
1908	Marine and Williams ⁸	Relationship of iodine to structure of thyroid gland was studied
1909	Dunhill ⁵⁴	Two stage operation for toxic goiter
1912	Hashimoto ⁶¹	Struma lymphomatosa described
1913	Mori ¹⁰⁰	Primary carcinoma of thyroid can cause hyperthyroidism
1914	Gudernatsch ⁶⁵	Thyroid feeding markedly increased metamorphosis in tadpoles but retarded somatic growth

1914	von Haberer, ¹⁴³ Halsted ¹	Thymectomy for toxic goiter
1914	Hertoghe ⁶³	Anginal pain noted in myxedematous patients
1914	McCarrison ⁹⁷	Pathogenesis of experimentally produced goiter reported
1915	Cannon, Binger and Fitz ¹⁸	Symptom complex of Graves's disease developed in a cat after suture of superior cervical sympathetic to phrenic nerve
1915	Halsted	Roentgen therapy over thymus for Graves's disease
1915	Kendall ⁷³	Crystalline thyroxin isolated
1916	Smith ¹³³	Hypophysectomy produces thyroid atrophy
1917	Marine and Kimball ⁷⁷	Iodine used for prevention of simple goiter
1918	Allen, ³ Hoskins and Hoskins ¹ (independently)	Metamorphosis and development of skeleton prevented in tadpoles by thyroidectomy
1918	Luden ⁸	Blood cholesterol is elevated in myxedema
1918	Zondek ¹⁵⁵	Description of 'myxedema heart'
1919	Goetsch ⁴⁴	Epinephrine sensitiveness in hyperthyroidism suggested as a diagnostic aid
1920	Loeb ⁸³	Thyroid tissue may respond with increased activity to a deficit or excess of iodine
1921	Shapiro and Marine ¹³⁰	Adrenal cortices from oxen benefited patients with toxic goiter
1922	Marine and Baumann ⁹¹	Adrenalectomy or freezing adrenal cortices in rabbits produced clinical picture of Graves's disease
1922	Murray ¹⁰⁰	Exophthalmos due to edema of tissues
1922	Smith and Smith ¹³¹	Pituitary elaborates a hormone which stimulates the thyroid
1923	Plummer and Boothby ¹¹	Iodine used for preoperative treatment of exophthalmic goiter
1924	Lahey and Hamilton ⁶⁰	The term 'thyrocardiac' coined
1925	Craver ²⁸	Irradiation of thyroid for carcinoma
1926	Harington ⁷	Thyroxin is a derivative of tyrosine
1926	Uhlenhuth and Schwartzbach ¹³⁷	Acid extracts of pituitary stimulated the thyroids of salamanders
1927	Harington and Barger ⁸	Synthetic thyroxin discovered
1928	Chesney, Clawson and Webster ²⁰	Cabbage has goitrogenic properties
1928	Rienhoff and Lewis ¹⁰⁹	Thyroid histologic changes during remission of hyperthyroid patient described
1929	Harington and Randall ⁹	Diiodotyrosin isolated from thyroglobulin
1930	Aron ⁴	Urine of toxic goiter patients contains less thyroid stimulating principle than normal
1930	Harington and Salter ⁶⁰	Thyroid hormone stored in gland as colloid
1930	Mason, Hunt and Hurxthal ⁹³	Blood cholesterol shown to fluctuate with thyroid function
1931	Abelin	Diiodotyrosin prepared
1931	Loeb and Friedman ⁸⁴	Chronic treatment with anterior pituitary thyrotropic extract resulted in a state of refractoriness to the effects of the injected substance
1931	Schockaert ¹¹⁸	Exophthalmos demonstrated in ducks following thyrotropic hormone injections
1932	Aron and Benoit	Serum and urinary thyrotropic hormone are increased in thyroidectomized animals

1932	Marine Spence and Cipra ⁹¹	Injections of methylcyanide caused chronic bilateral exophthalmos in rabbits
1932	Naffziger and Jones ¹⁰	Fibrosis and lymphocytic infiltration of degenerated muscles resulted in exophthalmos bilateral orbital decompression advised
1933	Blumgart, Levine and Berlin ¹	Angina pectoris and congestive heart failure treated by thyroidectomy
1933	Marine and Rosen ⁹²	Anterior pituitary extracts produced exophthalmos in thyroidectomized guinea pigs
1934	Drouet ³³	Graves's disease was due to hyperpituitarism (an excess of thyrotropic hormone) with resulting hyperthyroidism
1934	Elmer and Scheps ³¹	Blood iodine parallels basal metabolic rate
1934	Etienne and Drouet ³⁷	Deep roentgen therapy of pituitary for Graves's disease
1935	Zeckwer Dawson Keller and Livingood ¹	Stunting of growth in the cretin rat might be due to a decrease in acidophilic cells of the pituitary
1938	Hertz Roberts and Evans ⁸ Hamilton ¹	Radioactive iodine studied as an indicator of thyroid physiology
1939	Hamilton and Soley ³⁵	Iodine metabolism analyzed by radioactive isotope in different types of thyroid disease
1940	Hamilton Soley and Eichorn ¹	Radioactive iodine uptake in carcinoma of the thyroid was reported
1941	Mackenzie Mackenzie and McCollum ⁹⁶	Sulfaguanidine has goitrogenic effects
1941	White and Ciereszko ¹	Thyrotropic hormone purified
1942	Hamilton and Lawrence also Hertz and Roberts ⁴¹	Radioactive iodine therapy for hyperthyroidism
1942	Heston Ball Frantz and Palmer ⁷⁴	First positive evidence of pickup of radioactive iodine by a metastatic lesion from a carcinoma of the thyroid
1943	Astwood ⁹	Thiouracil depressed the production of thyroid hormone and was effective in treatment of hyperthyroidism
1943	Griesbach and Purves ⁴⁷	Thyrotropic content of pituitary diminished in proportion to the decrease in acidophilic cells in thyroidectomized rats serum thyrotropic hormone was increased
1947	Cope Rawson and McArthur ⁶	Hypersecretory solitary adenoma proved by radioactive iodine studies

II ANATOMY

A LOCATION

- 1 A bilobed encapsulated gland
 - a Lying on either side of the trachea
 - b Extending from the second to the fourth tracheal cartilage and occasionally to the first
- 2 Muscles covering it
 - a Sternocleidomastoid
 - b Sternohyoid
 - c Sternothyroid
 - d Omohyoid

B DESCRIPTION

- 1 Color
 - a Reddish
 - b Grayish brown
- 2 Consistency—slightly firm
- 3 Shape
 - a Smooth
 - b Irregular
 - c Anteriorly—convex
 - d Posteriorly—concave
- 4 Capsule sends thin fibrous septa into the stroma to form irregular incomplete lobulations

- 5 Thyroid and parathyroids may be within it
- 6 Accessory tissue may be present in
 - a Base of tongue (lingual thyroid)
 - b Neck
 - c Thyroglossal duct
 - d Thymus
 - e Mediastinum
 - f Struma ovarii

C PARTS (see Fig 113)

- 1 Isthmus
 - Connects the two lateral lobes of the thyroid (an H shape or butterfly)
- b May be
 - (1) Absent
 - (2) Separate from both lobes
 - (3) Varied in size, $\frac{1}{2}$ in in breadth and depth usually
- 2 Pyramidal process, a cordlike structure, arises from the isthmus which may
 - a Lie to left of midline in front of cricoid and thyroid cartilages
 - b Extend toward and up to hyoid bone
 - c Be
 - (1) Absent
 - (2) Double
 - (3) Separate from lateral lobes
 - (4) Any size

D WEIGHT

- | | Gm |
|--------------|---|
| 1 Newborn | 15 25 (0.06% of body weight) ⁸ |
| 2 Tenth year | 10 ³ |
| 3 Puberty | 15 ³ |
| 4 Adult | |
| a Range | 8 60 249 |
| b Average | 20 28 (0.4 Gm/Kg of body weight) ^{1 8} |
- 5 Right lobe is slightly larger than left
 - 6 Normal increase in size and weight at
 - a Puberty
 - b Premenstrual phase
 - c Pregnancy
 - d Menopause

E SIZE⁹

- | | CM |
|-------------|-------|
| 1 Length | 5 8 |
| 2 Width | 2 4 |
| 3 Thickness | 1 2 5 |

F BLOOD AND LYMPH SUPPLY

1 Arteries

- a Superior thyroids (one from each side) from external carotids
- b Inferior thyroids (one from each side) from subclavian vessels or thyrocervical trunk
- c Thyroid ima (fifth artery not constant) from arch of aorta or innominate
- d Aberrant arteries (collaterals) may originate from
 - (1) Tracheal
 - (2) Pharyngeal
 - (3) Esophageal
- e Vessels anastomose on the surface of gland
 - (1) Blood supply is abundant¹
 - (a) 3 5 6 cc/Gm of tissue/min (or 5 liters/hr for whole gland)
 - (b) Many anastomoses
 - (c) Blood vessels are large
 - (2) Capillary network encircles each follicle

2 Veins

- Commence as a perfollicular plexus
- b Follow small arteries
- c Empty as
 - (1) Superior thyroid (two usually) into internal jugular or common facial
 - (2) Inferior thyroid (two most frequently) into innominate or internal jugular
 - (3) Middle thyroid (not constant) into internal jugular
 - (4) Branch from pyramidal lobe into one of anterior jugulars
 - (5) Thyroid ima (one or two occasionally) into left innominate or venous angle

3 Lymphatic vessels

- a Form a rich plexus surrounding each follicle
- b Correspond to blood vessels
- c Drain into nodes of
 - (1) Deep cervical region
 - (2) Lateral and front portions of trachea
 - (3) Supraclavicular area
 - (4) Prelaryngeal
 - (5) Upper mediastinal (occasionally)
- d May empty directly into subclavian vein

G NERVES^{9 7 9}

- 1 Fibers follow arteries and end in dense networks surrounding each follicle
- 2 Nonmyelinated postganglionic fibers from middle and inferior cervical ganglia of sympathetic system
- 3 Parasympathetic fibers may come from
 - a Vagus
 - b Laryngeals
 - (1) Inferior
 - (2) Superior
 - (3) Recurrent (see Chart 27)
 - c Ansa hypoglossi
 - d Carotid plexus

III EMBRYOLOGY (development in weeks)^{2 8}

- A THREE (14 mm) — Entodermal lining thickens mesially into an evagination between the first and the second pharyngeal pouches
- B FIVE (55 mm)
 - 1 Bilobed sac with stalk develops
 - 2 Stalk (neck) a narrow tube is known as thyroglossal duct
- C SIX (11 mm)
 - 1 Solid epithelial plates form
 - 2 Evaginations from the fourth entodermal pouch give rise to the lateral thyroid components (questionable)
 - a These grow forward and upward to meet the posterior surface of the median lobe
 - b The three portions begin to fuse into one
 - 3 Thyroglossal duct
 - a Development—separates from pharynx and atrophies
 - b Point of origin on tongue remains permanently known as the foramen caecum
- D SEVEN (17 mm) — Single lobe lies on either side of trachea
- E EIGHT (25 mm)
 - 1 Follicle formation begins⁷
 - 2 Ingrowth of
 - a Connective tissue
 - b Blood vessels
- F ELEVEN TO FOURTEEN (60 to 100 mm)
 - 1 Secretory follicles appear^{1 6}
 - 2 Colloid develops^{7 21}
 - 3 Thyroxin is found⁸

- 4 Total iodine present in fetal thyroid glands varies from 1 to 19 micrograms from third to ninth month⁹
- 5 Radioactive iodine is collected by the thyroid¹

G TWENTY (160 mm) — Maximum number of follicles, thereafter growth in size only

IV CONGENITAL ANOMALIES

- A ABSENT (see 24) ^{4 6 11 1 11}
- B APLASIA (see 24) ^{4 8 11 10 11}
- C PYRAMIDAL LOBE (one third to one half of cases normally)^{9 1}
- D LINGUAL THYROID (see 35 \II H)^{10 13 17}
- E ABERRANT TISSUE^{2 9}
 - 1 Intrathoracic (see 18)
 - 2 Lateral (see 35 \II B)^{7 10 13}
- F TERATOMAS (containing thyroid tissue)
 - 1 Ovaries (see 78 IV) ^{8 1 16 19}
 - 2 Branchial clefts
- G THYROCLOSSAL DUCT (see 35 \II C) — Gives rise to
 - 1 Accessory thyroid glands
 - 2 Fistulae
 - 3 Cysts^{1 7}

V HISTOLOGY ^{3 13}

- A FOLLICLES (acini) (see Fig 114)
 - 1 Basic units
 - 2 Variations in
 - a Shape
 - (1) Ovoid
 - (2) Spherical
 - b Size—50 to 300 microns
 - c Number
 - 3 Lumina may be
 - a Small
 - b Large
 - 4 Lining of a single cellular layer resting on a very delicate reticular connective tissue (no basement membrane)
- B INTRAFOLLICULAR COLLOID (see 14 VI E 2 c)
 - 1 Amount present is variable depending on degree of thyroid activity
 - 2 Acidophilic stain taken by colloid which is more pronounced in center of follicle especially when epithelial cells are active
 - 3 Vacuolated appearance — scalloped edges with active transfer of colloid from follicle to cell or vice versa

C CELLULAR STRUCTURE (epithelium)

1 Types of cells

a Epithelial or 'chief'

(1) Resting stage

(a) Shape

[1] Cuboidal when cut perpendicular to base

[2] Polygonal tetrahedron or circular appearance when sectioned parallel with base

(b) Size (average)

[1] Base diameter—15 microns

[2] Height when cuboidal—15 microns

(c) Nucleus

[1] Large

[2] Spherical

[3] At base

(d) Colloid—rarely found

(e) Chromatin—poor

(f) Basement membrane—absent

(g) Function—secretory function slight, may be inactive (resting)

(2) Hyperactive stage

(a) Shape—columnar

(b) Size—height greater than 15 microns

(c) Nucleus—same as in cuboidal cell

(d) Colloid content—increases (globules)

(e) Other cellular elements—increase (see below)

(f) Function—few of these are present in normal resting gland

(3) Nonfunctioning stage

(a) Shape—flat

(b) Nucleus—pyknotic

(c) Cytoplasm—stains like colloid in some

(d) Cellular elements—decrease

(e) Function—probably none

b Parafoallicular (interstitial or intervesicular)¹⁴

(1) Location in intervalveolar spaces

(2) Belief is that they may be

(a) Embryonic cells which form new follicles

(b) Resting stage of glandular tissue

(3) Functions—possibly

(a) Absorption

(b) Secretory

(c) Formation of new acini

2 Cellular components

a Mitochondria¹¹

(1) Types

(a) Granules

(b) Filaments

(c) Rods

(2) Size and number increased with hyperactivity^{1, 10}

(3) Functions

(a) Intracellular surface may be increased by mitochondria, for lipoids can concentrate upon them

(b) If mitochondria disappear the lipoids return to the cytoplasm (decreased activity)

(c) Above changes may affect cellular permeability

b Golgi apparatus^{9, 11, 17}

(1) Reticular structure

(2) Position may indicate the direction of cellular secretion, if at¹³

(a) Apex—hypersecretion

(b) Base—hyposecretion

(3) Hypertrophy of the apparatus indicates increased activity

(4) Colloid droplets develop nearby with hypersecretion

c Oxidase granules are^{1, 16}

(1) Increased in size and number with cellular hyperactivity, opposite with hypofunction

(2) Seen in colloid with hyperactivity

(3) Indices of enzymic oxidation activity

d Alkaline phosphatase^{5, 7}

(1) Varies, but in an unknown manner

(2) Decreases after hypophysectomy

e Vacuoles

(1) Increase with cellular hyperactivity and vice versa

(2) Are considered to be artifacts by de Robertis (see Fig 117)⁸

- f Intracellular colloid
 - (1) Appears as droplets in apical portion of columnar cell
 - (2) Is rare in cuboidal cells

D CONNECTIVE TISSUE

- 1 Forms capsule which surrounds entire gland
- 2 Sends prolongations between the follicles (intrafollicular stroma) composed of
 - a Collagen
 - b Elastic fibers
- 3 Contains abundant
 - a Blood vessels
 - b Lymphatics
 - c Nerves

VI FUNCTIONS

A GLAND AS A WHOLE (see Chart 48 p 478)

- 1 Thyroid gland secretes and elaborates ingredients for the synthesis of thyroid hormone (which as yet has not been identified)
- 2 Thyroid hormone provides the necessary chemical and physiochemical stimuli to cellular processes which in total maintain the normal reaction and character of existence
- 3 Although nonessential to life it is indispensable for normal growth and development
- 4 Thyroid hormone inhibits the production of pituitary thyrotropic hormone (TSH)

B THYROID HORMONE (studied by giving thyroxin or desiccated thyroid similar effects are produced by thyrotropic hormone—see 2 VI B 5 14 VI C D)

- 1 Stimulation of
 - a All oxidative processes by effect on
 - (1) Permeability of cellular membrane
 - (2) Physiologic action on the cell surface
 - (3) Oxygen supply to tissues
 - b Normal somatic growth and development^{13 14 16 19 23 5 33}
 - c Nervous irritability
 - d Cardiac rate and output^{20 33 36 44 4}
 - e Blood volume^{2 34}
 - f Specific dynamic action of food stuffs

2 Metabolic influence

a Carbohydrate

- (1) Decrease in
 - (a) Liver and muscle glycogen^{1 37 41 40}
 - (b) Glucose and galactose tolerance
- (2) Increased¹¹
 - (a) Glycogenolysis
 - (b) Blood sugar (slight)
 - (c) Intestinal absorption⁸

b Fat

- (1) Direct action may be on fatty tissue
- (2) Indirect action is more likely by increased
 - (a) Expenditure of energy
 - (b) Muscular activity
- (3) Decreased blood^{20 1}
 - (a) Cholesterol
 - (b) Lipase¹

c Protein^{10 34}

- (1) Exogenous and endogenous breakdown—increased
- (2) Urinary excretion—increased¹⁸
 - (a) Nitrogen (no change in rats)
 - (b) Urea
 - (c) Creatine
- (3) Blood urea—decreased
- (4) Muscle creatinine (cardiac and skeletal)—decreased^{1 6 7 9 30 37}

d Water elimination—increased through¹

- (1) Kidneys
- (2) Bowels

e Miscellaneous

- (1) Urinary excretion—increased in
 - (a) Calcium, probably direct stimulation rather than through the parathyroids
 - (b) Phosphorus
 - (c) Iodine
- (2) Phosphatase content increased in
 - (a) Diaphyses
 - (b) Epiphyses
- (3) Blood iodine (organic or protein bound)—increased

C THYROIDECTOMY (Composite survey of human and animal observations—see also 14 VI VI)

1 Greatest changes in younger animal

- 2 Retardation of all metabolic processes, except elaboration of thyrotropic hormone
- 3 Cessation of ¹ ^m
 - Growth
 - b Development
- 4 Premature senility
- 5 Mental deterioration
- 6 Weight gain
- 7 Trophic disturbances of
 - a Skin
 - b Hair
 - c Osseous system
- 8 Body temperature reduced
- 9 Cardiac and nervous functions are suppressed
- 10 Lactation may or may not be affected¹⁹
- 11 Abdominal distention
- 12 Musculature (see 103 V)
 - Decreased content of
 - (1) Glycogen
 - (2) Fat
 - b Increased content of creatine in⁸⁴
 - (1) Cardiac
 - (2) Skeletal
 - c Hypotonicity
- 13 Reproductive system delayed²⁰ [†]
- 14 Liver glycogen increased⁶⁴
- 15 Intracellular edema increased, extracellular decreased
- 16 Protein stored in body fluids
- 17 Specific dynamic action of foods is lost
- 18 Urinary excretion—decreased
 - a Nitrogen
 - b Urea
 - c Creatine⁹⁴
 - d Calcium
 - e Phosphorus
 - f Iodine
 - g 17 ketosteroids
- 19 Blood chemical analyses
 - a Decreased
 - (1) Sugar (may be slight)⁷⁰
 - (2) Iodine
 - b Increased
 - (1) Urea
 - (2) Cholesterol¹⁷
 - (3) Lipase
- 20 Effect on other glands
 - a Pituitary
 - (1) Hypertrophy rarely atrophy in young

6	7	9	12	14	8	79	33		
2	37	4	44	46	48	1	5	33	90
60	69	7	7	76	78	79			

(2) Histologic changes—see 2 IX
 B 14³ 8 ⁷⁰ 4 6 34 44 50 55
 63 64 66 67 ■ 69 70 83 8

(3) Hormonal content
 (a) TSH—decreased or increased² ⁴
 (b) FSH—variable¹ 8 10 16 48
 ■ 1 7 73 7 8

(4) Thyrotropic hormone in
 (a) Urine—increased¹² 15 37 48
 (b) Serum—increased⁴ 43

(5) Growth hormone decreased
 (6) Diabetes insipidus⁴ ⁷⁷
 (a) Animals—variable results
 (b) Humans—improvement

b Parathyroids—data inconclusive
 c Adrenals

(1) Cortical size—variable⁴ 12 23
 30 31

(2) Epinephrine sensitivity—decreased⁴⁷

(3) 17 ketosteroid excretion—decreased

(4) ACTH response—decreased⁴

d Gonads

(1) Function—decreased¹⁰ 19 39-41
 47 57 61 60 7 74

(2) Weight⁶¹ 69 72

(a) No change

(b) Decreased (seminal vesicles especially)

(3) Sperm—decreased¹ 61 ■

(4) Ovulation—decreased¹⁰

■ Pancreas

(1) Diabetes mellitus improves¹

(2) No change in insulin sensitivity¹ 0

f Thymus—size variable 33 48 ■

D HYPERHORMONAL EFFECTS (see 14 VI VII)

1 On various organs and functions are summarized under

a Thyroid hormone

b Hyperthyroidism

c Factitious hyperthyroidism

2 On other endocrine glands

a Pituitary

(1) Size—decreased may be enlarged⁴ 7 15

(2) Histologic changes—see 2 VII B
 15⁴ 15 ■ 19

(3) Hormonal content

(a) TSH—decreased¹⁷

(b) FSH—variable⁴ 0 77

- (4) Thyrotropic hormone in¹
 - (a) Urine—absent
 - (b) Serum—decreased
- (5) Growth hormone increased (?)
(see 23 VI B)
- (6) Diabetes insipidus (see Proto
col 8 \IV)²³
 - (a) Animals—variable reports
 - (b) Humans—diuresis increased
- b Parathyroids—data inconclusive
- c Adrenals
 - (1) Cortical size—increased usually
4 5, 7 8 10 11 14 16 20 26
 - (2) Epinephrine sensitivity — in
creased^{7 14}
 - (3) 17 Ketosteroid excretion — de
creased
- d Gonads
 - (1) Function—decreased<sup>1 11 14 15
21 23</sup>
 - (2) Weight—variable seminal ves
icles decreased^{1 7 20}
 - (3) Sperm—decreased or no change¹
 - (4) Ovulation—decreased (?)
- e Pancreas
 - (1) Weight—increased^{6 7 12}
 - (2) Diabetes mellitus—made worse
- f Thymus—size variable may persist
3 7 8 1

E HISTOPHYSIOLOGY (see Figs 115 117)

- 1 Origin of secretion
 - a Thyroid hormone or its precursor
is manufactured and stored within
the thyroid gland
 - b Extrathyroidal source or synthesis
has been postulated (see 14 VI F
1 h)
 - c The level of thyroid activity is me
diated directly by the thyrotropic
hormone (TSH) of the pituitary
(see 2 VI B 5)
 - d The gland has an independent (of
pituitary) level of activity to
 - (1) Utilize iodine
 - (2) Form thyroid hormone
- 2 Concept of normal function
 - a Introduction
 - (1) The concept that the thyroid
gland secretes a hormone or its
precursor to fulfill the body
needs and stores the excess as
colloid is generally accepted
 - (2) Thyroid cells absorb inorganic
iodide which is

- (a) Synthesized into iodine
compounds (organic pro
tein bound)
- (b) Stored in the follicles as
colloid
- (3) When a demand exists for more
hormone, the colloid is
 - (a) Absorbed by the cells un
less irrevocably trapped
 - (b) Converted presumably into
hormone which is secreted
into the blood stream
- (4) The chemical form of the
iodine bearing compound or
compounds when secreted or
circulating in the blood stream
is unknown
- (5) It is possible that the true hor
mone is born only when the
iodine complexes escape into
the circulating blood
- (6) When the hormone supply is
adequate the gland is pictured
as storing colloid the cell polar
ity being central
- (7) When a demand for hormone
increase, the thyroid cells may
be considered temporarily at a
standstill until the reversal of
polarity takes place, the direc
tion of flow then is from the
follicle through the cells into
the blood stream or the lym
phatics¹
- (8) It is not likely that this re
versal of movement would affect
every follicle in exactly the
same degree at all times so that
only a few would be called
upon to supply a small increase
in demand¹
- (9) Wahlberg we conclude be
lieves that under normal condi
tions²⁰
 - (a) The vast majority of folli
cles are resting i.e. neither
secreting into the blood
stream or follicle
 - (b) Only a rare follicle supplies
the needed hormone and is
found in a secretory state
- (10) Radioactive iodine experiments¹⁵

- (a) Young animals (guinea pigs, rats)—all follicles are at same stage of activity
 - (b) Older animals—follicles differ in stages of activity
 - b Mechanism of iodide absorption, breakdown and utilization by the thyroid gland ^{7 9 11 13 16}
 - (1) Absorption of iodide and tyrosine from the blood stream by the thyroid epithelium
 - (2) Breakdown within the cell of iodide to free iodine by peroxidase an oxidative enzyme⁸
 - (3) Synthesis of diiodotyrosine, thyroxine and colloid as follows
 - (a) Formation of diiodotyrosine from free iodine and tyrosine (also from blood stream)^{1 12}
 - (b) Coupling of two molecules of diiodotyrosine to form thyroxine¹⁴
 - [1] This is possibly due to cytochrome oxidation system
 - [2] Manganese may act as a catalyst¹⁷
 - (c) Linkage of diiodotyrosine and thyroxine into large complex molecule as colloid
 - (d) Iodine may also be fixed in gland without diiodotyrosine and thyroxine formation
 - (e) Mobilization of colloid droplets at cellular apex (side facing follicle) is seen chiefly in hyperactivity
 - (f) Colloid molecule is too large for extrusion through cellular membrane^{3 4}
 - c Formation of follicular colloid
 - (1) Proteolytic enzyme of the thyroid cell breaks colloid droplets into smaller extrudable particles which are secreted into the follicle^{3 13 19}
 - (2) Intrafollicular colloid is largely thyroglobulin which must be formed by some intrafollicular system, the nature of which is unknown
 - (3) Iodine contained in the follicle is in the form of
 - (a) Diiodotyrosine—70 to 80 per cent
 - (b) Thyroxine—20 to 30 per cent
 - (4) Diiodotyrosine and thyroxine are linked together as thyroglobulin
 - (5) Oxidase granules appear in the intrafollicular colloid as if secreted from the cell and may be factors in thyroglobulin synthesis
 - (6) In abnormal states colloid
 - (a) May be
 - [1] Inactive (biologically i.e., hypothyroidism)¹⁴
 - [2] Stained poorly
 - (b) Is not strictly thyroglobulin, for it may lack
 - [1] Iodide
 - [2] Diiodotyrosine
 - [3] Thyroxine
 - d Resorption of colloid and secretion of hormone is regulated by a proteolytic enzyme which⁶
 - (1) Is secreted into the follicle
 - (2) Breaks down colloid into small particles that are
 - (a) Resorbed
 - (b) Passed to base of cell
 - (c) Secreted into capillaries
- F ACTIVITY AT DIFFERENT PERIODS IN LIFE
- 1 Intrauterine
 - a The placental role in the maternal fetal relationship is an important one in the production of
 - (1) Congenital goiter
 - (2) Cretinism
 - (3) Congenital athyreosis
 - b Placenta permits passage of
 - (1) Iodine ^{7 9 31}
 - (2) Goitrogenic agents ^{8 14 16 17 31 34}
 - (3) Thyrotropic hormone probably ^{9 34 41}
 - (4) Virus infections^{3 1 13 19 8 37}
 - c Passage of thyroid hormone through the placenta is unlikely for it is not found in
 - (1) Urine
 - (2) Milk
 - (3) Saliva
 - d Fetus may require little, if any thyroid hormone until the late stages of development^{6 10 11 24 25 8}

e A goiter may be produced in the fetus by

(1) Goitrogenic agents ^{8 11 16 31 31 31 4}

(2) Iodine lack ^{20 20 31}

1 Congenital rhythotics are born with a retarded bone age but are usually normal in size ^{10 15}

g The organic blood iodine of the umbilical cord is much lower than that of the mother suggesting that each has its own level of thyroid hormone ^{1 17 1}

TABLE 10 BLOOD IODINE IN MOTHERS AND NEWBORNS*

Case	TOTAL (WHOLE) BLOOD IODINE, MICROGRAMS %		ORGANIC (WHOLE) BLOOD IODINE MICROGRAMS %	
	Mother	Cord	Mother	Cord
1	0.0	55.0	65.7	29.6
2	33.8	53.0	26.7	8.0
3	72.8	41.3	36.9	12.2
4	60.0	22.8	41.5	9.6
5	22.8	68.2	19.4	8.5
Average	51.9	49.4	38.0	13.6

* We are indebted to Drs. Frederic C. Irving and E. A. Brubaker for procuring these blood samples.

h Myxedematous mothers may

(1) Improve during pregnancy ^{3 32 40 43} thus if thyroid hormone of fetus does not pass the placenta an extrathyroidal origin of hormone may be hypothesized possibly in the ovaries (see 100 I B 2) ^{1 4 8 7 17 22 6 30 30 30}

(2) Give birth to

(a) Cretins with or without goiters

(b) Normal children

i Hyperthyroidism and pregnancy—see 21

j Thyroid activity occurs before cell differentiation takes place in pituitary ⁷⁷

2 Infancy and childhood—continuation of thyroid function from intra uterine life with gradual increase in hormone production to meet the needs for growth and development

3 Puberty—a spurt in thyroid activity is thought to occur for the physiologic

changes with development in sexual function and body demands

4 Adult—secretion of thyroid hormone is related to general physiologic requirements

a Premenstrual phase—thyroid may enlarge and show increased activity

b Pregnancy—thyroid function gradually increases to meet the extra demands

c Temporary increased function is mediated through hypothalamus and pituitary (section of pituitary stalk prevents this in animals), with subsequent return to normal in most individuals with

(1) Emotion

(2) Cold

(3) Shock

(4) Exercise

5 Climacteric—thyroid function increases for a while and then decreases to correspond with the slowing down of bodily function

6 Old age—further retardation of all processes is followed by a similar decrease in thyroid function

G ANTITHYROID DRUGS

1 Experimental administration of thiouracil in animals and humans

a Thyroid effects—see 14 I A B 1 d

b Pituitary—see 2 I A B 22 k

c Growth retardation ³

d Adrenal cortices atrophy¹

e Liver⁴

(1) Weight—increased

(2) Fat and cholesterol—unchanged

(3) Glycogen—increased

f Fate^{8 12}

(1) Gastrointestinal absorption is rapid

(2) Distribution

(a) Tissues greatest in

[1] Thyroid

[2] Ovaries

[3] Pituitary

[4] Bone marrow

[5] Liver

(b) Body fluids

(3) Storage in thyroid is¹⁻

(a) Increased by TSH

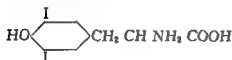
(b) Decreased by potassium iodide

- (4) Concentration—same in blood and thyroid gland
- (5) Destruction is swift
- 2 Excretion of thiouracil (200 mg) in normal human⁵⁻¹¹
 - a Urine
 - (1) Detectable in 30 min
 - (2) Maximum in 1 to 2 hrs
 - (3) None in 48 hrs
 - b Blood (fasting)
 - (1) Detectable in 15 min
 - (2) Maximum in 30 min
 - Feces—none

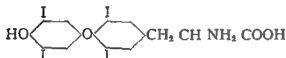
VII CHEMISTRY

A COLLOID

- 1 Each follicle contains different amounts
- 2 A thyroglobulin (molecular weight 700,000^{3, 4}) which yields two fractions in variable proportions (see below)
 - a "D" fraction (75%)—diiodotyrosine-like
 - b "T" fraction (25%)—thyroxine-like
- 3 Formulas of the two amino acids
 - a Diiodotyrosine



- b Thyroxine (synthesized)²



- 4 Physiologic activity of contents
 - a Thyroglobulin Active (more so than thyroxine)
 - b Thyroxine (dextro and levo) Both equally active
 - c Diiodotyrosine Inactive unless part of thyroglobulin molecule⁹

B THYROID HORMONE

- 1 Structure
 - Exact nature unknown the hormone is a portion of the colloid molecule
 - b Thyroid hormone or thyroglobulin

has not been demonstrated in the blood stream^{6, 16, 17}

- c Discharged thyroid hormone may be peptide of 1 thyroxine
- d Diiodotyrosine comprises only 10 per cent of plasma iodine¹⁷
- e Organic or plasma bound iodine may be index or indirect measure of circulating hormone in the blood
- 2 Daily output
 - a Estimated secretion of thyroid hormone or its equivalent in thyroxine is 0.33 mg¹⁰
 - b The amount of desiccated thyroid needed by myxedematous adults is used as the basis for normal hormonal requirement
 - (1) Average maintenance dose is 1½ to 2 gr of desiccated thyroid (USP)
 - (2) 1½ gr of desiccated thyroid (USP) contains 220 gammas of iodine or 0.22 per cent of organic iodine
 - c It is not found in
 - (1) Urine
 - (2) Milk
 - (3) Sweat
- 3 Mode of action on end organs
 - a Unknown
 - b Catalytic (enzymic) action at cell surface suggested by Zondek^{18, 19}
- 4 Extrathyroidal deposits of thyroid hormone ("D" and "T" fractions of organic or colloidal iodine demonstrated)¹¹
 - a Ovaries—may synthesize it, especially during pregnancy^{1, 8, 12}
 - b Muscles—concentration rises and falls with thyroid function^{1, 8, 12, 13}
 - c Liver¹³
 - d Intestines¹¹
 - Kidneys¹³
- 5 Blood stream—serum protein when iodinated in vitro and administered to humans relieves myxedema this does not occur in vivo in humans,^{7, 14, 15} but may in animals⁵

VIII BIO ASSAY

- A INTRODUCTION—Tests to determine physiologic potency of
 - 1 Desiccated thyroid
 - 2 Thyroxine

- 3 Preparations of unknown biologic activity
- II GUDERNATCH TADPOLE TESTS⁴
 - 1 Normal larvae can metamorphose within 18 hrs by feeding thyroid tissue rather than the usual 10 to 12 weeks
 - 2 Thyroidectomized larvae
 - a Do not metamorphose, but can grow larger in size
 - b Given thyroid, they will develop at a normal rate
 - 3 Inorganic iodine fed to thyroidectomized tadpoles produces same results¹¹
 - 4 Axolotls may be used instead
 - 5 Effect of thyroxin on growth of white rats and rabbits can be determined¹²
- C ACETONITRIL TEST⁸
 - 1 Mice (or guinea pigs) are fed thyroid equivalent to 7 per cent of food intake for 2 to 14 days (usually 7 days)
 - 2 Acetonitril dissolved in water is injected subcutaneously
 - 3 Fatal dose for controls is 0.32 mg/Gm of mouse
 - 4 Minimal fatal dose of acetonitril is not less than 1.4 mg/Gm of mouse
 - 5 Sensitivity of test—1 mg of desiccated thyroid mixed 40 000 times its weight of cracker diet can be detected
- D OXYGEN CONSUMPTION TESTS
 - 1 Oxygen consumption of rats (rabbit dog guinea pig with or without thyroid gland may be used)^{3, 10}
 - a Special apparatus for study of gaseous metabolism of rats (or other animals) is required
 - b Definite criteria for the experiment are followed (i.e., room temperature diet, etc.)
 - c Adequate dose of thyroxin is injected subcutaneously or desiccated thyroid is given orally
 - d Oxygen consumption increases after 18 hrs with a maximum in 48 hrs
 - The resting oxygen consumption at 25° is 14.44 ± 0.07 cc/kg/mm or 700 calories/sq m/24 hrs
 - f Percentage increase is calculated by comparison of (a) and (e)
 - 2 Oxygen consumption in athyreotic humans⁹
 - a Patients with definite untreated spontaneous myxedema are used in which metabolism rate is constant (average minus 38%)
 - (1) Men between 20 to 50 years of age average 23.5 calories/sq m/hr
 - (2) Women of these ages average 22.0 calories/sq m/hr
 - b The preparation to be tested may be given
 - (1) Orally or intravenously
 - (2) Single massive or divided doses
 - c Daily rise in basal metabolic rate is observed
 - (1) Average slope (oral administration) is 2.5 points/24 hrs
 - (2) Single dose produces a peak on the fifth day
 - (3) Divided doses cause a maximum rise by the twelfth day
 - d Every subject when given identical amounts of hormone will show the same rate and rise in basal metabolic rate
 - e Calorigenic activity of whole thyroid is related to the amount of organic iodine, not the thyroxin iodine
 - f Test gives accurate results but is impractical for routine assay
- E CHEMICAL ASSAY⁵
 - 1 A suitable amount of material usually 25 tablets, each equivalent to 5 gr of fresh thyroid gland, are
 - a Ground and suspended in 10 parts of normal sodium hydroxide solution
 - b Boiled under reflux condenser for 4 hrs
 - 2 Hot solution is filtered quantitatively from traces of inorganic material and an aliquot portion is analyzed for iodine
 - 3 Total iodine content of original samples is calculated
 - 4 Remainder of filtrate is adjusted to a pH of 5.0 by addition of 50 per cent sulfuric acid and left overnight
 - 5 Second quantitative filtration is done
 - a Filtrate analyzed again for iodine
 - b Difference between first and second analyses gives value of the acid insoluble or thyroxin iodine
 - 6 Another 50 gr of desiccated thyroid is ground with 10 cc distilled water
 - a Mixture is filtered

TABLE 11 SURGICAL PATHOLOGY OF THE MORE COMMON DISEASES

	SIZE	APPEARANCE	CAPSULE	CONSISTENCY	LOCATION	EXTENSION
Diffuse hyperplasia	Normal to 10 times or more usually 3 to 4 times	Lobulated covered with veins reddish brown isthmus and pyramidal lobe always demonstrable	Tense held firmly	Elastic to firm	Normal	None always in the neck unless edematous changes extend into superior straight
Multiple nodular	Increased 2 times or more may be large	Nodular cystic fibrotic bands between the lumps brown vascularly variable but not marked	Tense intact	Variable in different parts of gland	Usual or rarely an intrathoracic aberrant thyroid	Into superior straight or mediastinum sometimes not invasive
Riedel struma	to 3 times normal in most	Asymmetrical gray color	Tight in parts tissue planes fused	Very hard	Normal	Adherent to trachea and muscles displaced with great difficulty
Hashimoto's struma	Slight to moderate	Diffuse bilateral contour of gland recognizable	Preserved	Firmer than normal	Normal	May surround trachea
Adenoma (nodule)	1 to 6 cm in diameter	Asymmetrical variable color reddish brown if hemorrhage	Definite	Soft to hard	Any part of gland	Usually above superior trachea
Adenoma with blood vessel invasion	Small to large	As any adenoma (see above)	Intact	Soft to hard	Normal	Lungs and bones
Papillary carcinoma	Variable	May be cystic or hemorrhagic	May be broken	Firm	Lateral areas of thyroid	May be adherent to muscle
Diffuse carcinoma	Variable	Vascularly increased white	Invasion marked destruction	Hard	Neck superior to aight on mid trachea	Adherent to muscle invasion of a lymphatic node

- b Filtrate contains only inorganic iodine 5 cc used for quantitative analysis and should not exceed 10 per cent of total iodine
- c Residue containing iodothyroglobulin is
- (1) Physiologically active
 - (2) Used for standardization
- 7 Desiccated thyroid should contain 0.09 \pm 0.01 per cent of thyroxine iodine
- 8 U.S.P. standard—tablets must contain amounts of iodine not less than 0.17 per cent and not more than 0.23 per cent of the labeled amount of thyroid

F OTHER TESTS

- 1 Rate of
 - a Carbon dioxide production (mice)
 - b Oxygen consumption (rats)
- 2 Increased sensitivity of rats to oxygen deficiency may be used as an index

IX PATHOLOGY

A Gross—See Tables 11 and 12

TABLE 12 THYROID DISEASES FOUND IN TOTAL NUMBER OF THYROID GLANDS EXAMINED (SURGICAL SPECIMENS) AT THE NEW ENGLAND DEACONESS HOSPITAL FROM 1927 THROUGH 1947 (DR SHIELDS WARREN)

Primary hyperplasia	10	26
Multiple colloid adenomatous goiter		10 964
Among these with secondary degenerative hyperplasia	1,586	
Colloid storage goiter		140
Adenomas	1,893	
Fetal		807
Simple		383
Embryonal		183
Colloid		160
Unclassified		125
Papillary cysts		107
Multiple		74
Toxic		33
Hürthle cell		23
Other benign tumors	53	
Cysts		33
Lipoma		13
Fibroma		7
Aberrant	33	
Lateral		31
Lingual		2
Inflammatory	362	
Thyroiditis acute and chronic		226
Hashimoto's struma		105
Piedel's struma		26
Tuberculo		5

Malignant	436	
Papillary cystadenoma		127
Papillary adenocarcinoma		80
Adenocarcinoma		67
Embryonal adenoma		28
Carcinoma simplex	116	
Small cell		80
Giant-cell		36
Carcinoma unclassified		13
Hürthle cell carcinoma		5
Miscellaneous cancers	10	
Epidermoid		4
Fibrosarcoma		3
Lymphoma		3
Various conditions		221
Total		74 00

II MICROSCOPIC AND HISTOPHYSIOLOGY

1 Experiments (animals)

a Thyrotropic hormone (TSH)²⁰

- (1) Excess (by injection) causes an increase in the thyroid gland of the
 - (a) Height and proliferation of the cells
 - (b) Mitochondria
 - (c) Golgi apparatus
 - (d) Absorption of iodides by the cells
 - (e) Cellular peroxidase and follicular colloid which hasten the processes listed above i.e. synthesis of diiodotyrosine and thyroxine
 - (f) Proteolytic enzyme which promotes^{21 22}
 - [1] Secretion of colloid droplets into follicle
 - [2] Greater absorption of follicular colloid
 - (g) Colloid droplets at the base of the cells for release into the blood stream²³
- (2) Its inactivation (not destruction) by different thyroid biopsy specimens has been determined²²

TSH—UNITS

- (a) Normal 3-4
- (b) Hypofunction 0 (probably)
- (c) Hyperplasia 7-8
- (d) Single hypersecretory adenoma

- [1] Hyperplastic portion 7 8 TSH—UNITS
- [2] Atrophic section Less than 1
- (3) Essential to form goiter^a
- b Iodine in excess (therapeutic amounts)
- (1) Thyrotropic hormone^{1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
- (a) Inactivation usually
- (b) Pituitary content increased (with large doses)
- (2) Thyroid^{13 17 18}
- (a) Proteolytic enzyme may be decreased directly or indirectly through the pituitary
- (b) Absorption of intrafollicular colloid by the cells for hormone synthesis and secretion is decreased
- (c) Peroxidase is not affected
- (d) Colloid (with involution) is
- [1] Synthesized continually
- [2] Transferred to follicle
- [3] Trapped there
- c Radioactive iodine (orally administered)^{6 11 30 31 3 3 4 47}
- (1) Uptake by thyroid varies with the following
- (a) Dosage
- (b) Previous iodination
- (c) Ingestion of desiccated thyroid
- (d) Degree of secretory activity
- (e) Type of gland⁶⁰
- (f) Presence of antithyroid medication in gland as well as type of drug
- (g) Other factors
- [1] Stress
- [2] Diet
- [3] Exposure to cold
- (2) Location of trapped radioactive iodine
- (a) Largest amount found in colloid of
- [1] Hypersecretory hyperplastic thyroid
- [2] Diffuse colloid goiter with euthyroidism
- (b) Greatest amount in cells of

goiter associated with hypothyroidism

(c) Adenomas take up less than surrounding tissue in non-toxic nodular goiter

- (3) Radioactive iodine studies do not correlate well with degrees of clinical hyperthyroidism⁷³
- (4) Résumé of absorption and urinary excretion in normal subjects and various types of thyroid disease (only approximate values can be outlined as dosages and methods of experiments differ—see Table 13, Charts 28 and 29)

TABLE 13 RADIOACTIVE IODINE ADMINISTRATION^{3 7 1 23 24 25 26 31 32, 37 40 43 60 65 68}

TYPE OF THYROID GLAND	PER CENT OF ABSORPTION BY THYROID	PER CENT OF URINARY EXCRETION WITHIN 48 Hrs
Normal	20-40	60-80
Hypersecretory diffuse hyperplastic*		
Untreated	80-90	10-20
Iodine treated	1-7	80-90
Thiouracil prepared	10-20	80-90
Nodular goiter		
Toxic no iodine	3-7	85-90
Nontoxic	10-20	49-75
Myxedema		
Without goiter	?	75-80
With goiter	Probably 10-20	49-75
Surgical	0	80-90
Thyroiditis	Diminished	
Cancer (15%)	Variable	

* In view of the differences in urinary iodine in hypersecretory hyperplastic thyroid of short duration (greater) and of long duration (less) it is obvious that the output of iodine in these experiments would be influenced by this phenomena

d Thiouracil (see Fig 119)^{4 5 8 1 16 41 4 80 8 7 61 63 71}

- (1) Peroxidase system is depressed thus retarding
- (a) Liberation of free iodine
- (b) Synthesis of hormone (diiodotyrosine and thyronine formation prevented none in cells or colloid)

- (2) Proteolytic and cytochrome oxidase enzymes are unaffected as hormone is discharged until exhausted
 - (3) Marked hyperplasia of thyroid cells
 - (4) Vascularity increased
 - (5) Involution with colloid storage takes place if iodine is given in sufficient amounts but new hormone is not made or secreted¹
 - (6) Radioactive iodine is inhibited⁶ and prevented from penetrating follicles⁹ ~ 69-61
 - (7) Prolonged administration produced histologic appearance of adenocarcinoma in rats⁷ 50
 - e Sulfonamides³ 6
 - (1) Competitive attachment of these drugs to liberated iodine (see below) preventing synthesis of
 - (a) Diiodotyrosine
 - (b) Thyroxine
 - (2) Peroxidase increased in cells but not in colloid
 - (3) Other enzymes are not depressed
 - f Potassium thiocyanate (when given over prolonged periods to susceptible individuals) (see Fig 118)
 - (1) Myxedema may develop
 - (2) Mild hyperplasia produced
 - (3) Conversion of iodine to D and T fractions depressed
 - (4) Gland takes up 76 per cent of tracer doses of radioactive iodine
 - (5) Iodine administration will prevent goiter in animals
 - g Various other agents on thyroid slices
 - (1) Inhibit formation of D and T fractions
 - (a) Cyanide
 - (b) Azide
 - (c) Sulfides
 - (d) Carbon monoxide
 - (e) Sulfonamides
 - (f) Iodides
 - (g) Thiourea
 - (h) Thiouracil
 - (i) Allyl thiourea
 - (j) Para aminobenzoic acid
 - (k) Potassium thiocyanate
 - (2) Prevent uptake of iodine
 - (a) Cyanide
 - (b) Sulfides
 - (c) Potassium thiocyanate
 - (3) Do not prevent iodine accumulation
 - (a) Sulfonamides
 - (b) Thiourea
 - (c) Thiouracil
 - (d) Allyl thiourea
 - (e) Para aminobenzoic acid
 - h Nerve stimulation (superior laryngeal)—increase in⁷
 - (1) Cellular height
 - (2) Mitochondria
 - (3) Golgi apparatus
 - (4) Vacuoles
 - (5) Hormone discharge
 (Findings are not conclusive inasmuch as stimuli may reach pituitary or adrenals both of which can cause such changes)
 - i Hypophysectomy¹⁰
 - (1) Results—decrease in
 - (a) Cellular height
 - (b) Mitochondria
 - (c) Golgi apparatus
 - (d) Absorption of iodides
 - (e) Proteolytic enzyme (see above)
 - (2) Peroxidase may not be affected because diiodotyrosine fraction is synthesized (although not the thyroxine fraction)⁶⁴ 70
 - (3) Colloid stored in follicle relatively inactive (D fraction)
 - (4) Less than normal amounts of thyroxine in thyroid gland⁴ 70
 - j Miscellaneous
 - (1) Inanition produces same effects as hypophysectomy⁶⁹
 - (2) High protein diet does not cause thyroid hypertrophy this may be factor in production of thyroid deficient pigs³³ 44 67
- ## 2 Clinical states
- a Colloid adenomatous goiter with euthyroidism
 - (1) Epithelium
 - (a) Inactive mostly
 - (b) Active portion has colloid droplets only at apex

- (2) Colloid may be
 - (a) Deficient in thyroxin factor
 - (b) Inactive
- (3) Mitochondria and Golgi apparatus
 - (a) Are decreased
 - (b) May go into follicle
- (4) Peroxidase granules are not increased
- (5) Proteolytic enzyme is less active in these cells, permitting colloid secretion into follicle, but not reabsorption^{13 17}
- (6) Thyroid administration may decrease glandular size
- (7) Iodine may cause thyroid deficiency by³⁹
 - (a) Increasing storage
 - (b) Decreasing hormone secretion
- b Myxedema
 - (1) Atrophy of thyroid gland
 - (a) Few follicles may remain, some of which are hyperplastic
 - (b) Scar tissue
 - (c) Hyaline degeneration
 - (d) Lymphocytic infiltration
 - (e) Hormone is insufficiently synthesized
 - (f) Radioactive iodine uptake does not occur
 - (2) Thyroiditis of various types—replacement of follicles by lymphoid or sclerotic tissue
 - (3) Colloid adenomatous goiter
 - (a) Fetal adenoma may be present with or without some hyperplastic follicles
 - (b) Colloid follicles with flattened epithelium are numerous
 - (c) All normal uninvolved tissue may be
 - [1] Greatly compressed
 - [2] Nonfunctioning (no actual data here)
 - (4) Diffuse enlargement (clinically colloid or hyperplastic large follicle hyperplasia)⁴³
 - (a) Colloid secretion into follicles
 - (b) Epithelial
 - [1] Hyperplasia
 - [2] Proliferation
 - (c) Hormonal output in variable amounts (see 17)
 - (d) Thyroid administration
 - [1] Myxedema relieved if present
 - [2] Gland may decrease in size, possibly through
 - [a] TSH inhibition
 - [b] Decreased hyperplasia
 - (e) Iodine administration
 - [1] Hormonal secretion may be decreased, if normal previously (rare)
 - [2] Myxedema may follow (infrequent)
 - [3] Basal metabolic rate rise has been reported²⁴
 - [4] Gland itself will take up radioactive iodine
- c Hyperthyroidism (hypersecretory diffuse hyperplastic thyroid)
 - (1) Changes are present ■ noted under histology due to hypersecretion (see 14 V C 2)
 - (2) Cells
 - (a) Number—increased
 - (b) Colloid particles—larger
 - (c) 'Vacuoles' in basal portion as compared with apex, suggest greater hormone synthesis and secretion (reversal of polarity)
 - (3) Colloid in follicles may be completely reabsorbed but central portion of the remaining colloid in other follicles may stain dark before complete absorption (indicating thick concentrated colloid—see Fig 120)
 - (4) There is an increase in
 - (a) Vascularity of interfollicular tissue
 - (b) Proteolytic enzyme of follicle^{1 18}
 - (c) Peroxidase activity
- d Nodular goiter with hyperthyroidism
 - (1) Introduction
 - (a) Histologic picture may be divided into three main groups

- (b) Thyroid cells show changes depending on their state of function
- (2) Nodules which appear functionally autonomous and not hypersecretory
 - (a) Colloid has less iodine and thyroxine fraction than surrounding tissue
 - (b) Cont. at mostly diiodotyrosine factor
 - (c) Surrounding tissue is hyperplastic and source of excess hormone
 - (d) Radioactive iodine taken up slowly⁴⁵
 - (e) Fetal adenoma also less active⁴³
- (3) Nodules which appear partially hypersecretory
 - (a) As the disorder progresses periphery of adenoma may have
 - [1] Colloid loss
 - [2] Hormone secretion in excess
 - (b) Entire adenoma finally may be hypersecretory with typical hyperplasia
 - (c) Iodine may penetrate adenoma causing colloid storage in periphery a reversal of the process by which it becomes hypersecretory
 - (d) Thyroxine fraction presumably increased⁷⁷
- (4) Hypersecretory discrete nodule or nodules with surrounding atrophic thyroid tissue
 - (a) Radioactive iodine taken up more readily⁵¹
 - (b) Iodine has less therapeutic value possibly because of dense capsule which retards penetration
 - (c) Adenomatous tissue shows
 - [1] Twice the power to inactivate thyrotropic hormone than does normal tissue
 - [2] Similarity to hyperplastic tissue

- [3] An increase in
 - [a] Thyroxine fraction
 - [b] Proteolytic enzyme
- (d) Removal restores normal basal metabolic rate

X CLASSIFICATIONS

A COMPREHENSIVE LIST OF CHIEF FACTORS IN ENDOCRINE DISEASES—see 2 \ A

II HORMONAL

1 Introduction

- a The hormonal status in thyroid disease may vary from hypofunction to hyperfunction in the same individual depending on the natural course of the disorder
- b For example the development of hyperthyroidism in a goitrous cretin from therapy
- c Any hormonal classification therefore refers only to the situation at hand

2 Normal—euthyroidism

3 Hyposecretion

- a Cretinism
- b Myxedema

4 Hypersecretion—hyperthyroidism

C CLINICAL

1 Introduction

- a Thyroid function may bear little relationship to the type of disease present within the gland except when thyroid tissue is absent or profoundly deficient
- b Generally however there is clinical correlation

2 Euthyroidism

- a Normal thyroid function with or without thyroid enlargement of any type
- b Exophthalmic syndrome

3 Cretinism

- a At or before birth
 - (1) Congenital absence of thyroid—synonyms
 - (a) Congenital athyreosis
 - (b) Thyroaplasia
 - (c) Sporadic cretinism without goiter
 - (2) Congenital goiter
 - (3) Endemic goiter
- b Infancy and childhood
 - (1) Congenital goiter

- (2) Colloid or colloid nodular goiter (endemic)
- (3) Hyposecretory diffuse hyperplastic goiter
- (4) Thyroid atrophy
- (5) Thyroiditis
- (6) Surgical ablation
- 4 Myxedema
 - a Synonyms
 - (1) Gull's disease
 - (2) Primary thyroid
 - (a) Deficiency
 - (b) Atrophy
 - (3) Hypothyroidism
 - (4) Athyreosis
 - b Colloid or colloid nodular goiter (endemic)
 - c Hyposecretory diffuse hyperplastic goiter
 - d Thyroiditis
- 5 Hyperthyroidism
 - a Hypersecretory diffuse hyperplastic goiter—synonyms
 - (1) Parry's disease
 - (2) Graves's disease
 - (3) Basedow's disease
 - (4) Exophthalmic goiter
 - (5) Primary hyperthyroidism
 - (6) Thyrotoxicosis
 - (7) Toxic hyperplastic goiter
 - b Nodular goiter and superimposed hypersecretory hyperplasia in remainder of gland, synonym—adenomatous or nodular goiter with superimposed Graves's disease or secondary hyperthyroidism
 - c Hypersecretory nodular goiter—synonyms
 - (1) Adenomatous goiter with hyperthyroidism
 - (2) Nodular goiter with hyperthyroidism
 - (3) Multiple colloid adenomatous goiter with hyperthyroidism
 - (4) Toxic nodular goiter
 - (5) Toxic adenomatous goiter
 - d Hypersecretory solitary nodule within a hyposecretory gland—synonyms
 - (1) Hyperfunctioning adenoma
 - (2) Hyperfunctioning solitary nodule
 - (3) Toxic adenoma
 - (4) Plummer's disease
 - e Factitious—synonyms
 - (1) Self induced
 - (2) Alimentary
 - (3) Thyrotoxicosis factitia
 - f Coincidental disease of thyroid gland with superimposed hypersecretory hyperplasia
 - g Recurrent or persistent
 - (1) Hyperthyroidism—any type
 - (2) Colloid goiter
 - (3) Nodular goiter
 - h Thyrocardiac disease—any type of hyperthyroidism

D TUMORS

1 Benign

- a Colloid
 - (1) Goiter
 - (2) Nodular (or endemic) goiter
 - (3) Cyst
- b Diffuse normosecretory hyperplastic goiter
- c Thyroiditis
 - (1) Nonspecific
 - (2) Hashimoto
 - (3) Riedel
 - (4) Amyloid
 - (5) Syphilitic
 - (6) Tuberculous
- d Lingual thyroid
- e Lateral aberrant thyroid
- f Adenoma
 - (1) Fetal
 - (2) Embryonal
 - (3) Simple
 - (4) Multiple
 - (5) Hurthle cell

2 Malignant

- a Benign metastasizing
- b Malignant adenoma
 - Papillary adenocystoma
- d Papillary adenocarcinoma
- e Carcinoma
 - (1) Simplex
 - (2) Alveolar
 - (3) Giant cell
 - (4) Hurthle cell
- f Metastatic nodule—extrinsic
- g Miscellaneous types

XI and XII CHIEF CLINICAL FINDINGS OF HYPOSECRETION AND HYPERSECRETION

	HYPOSECRETION (PRIMARY THYROID DEFICIENCY, NOT FROM ABSENT TSH)	HYPERSECRETION (FROM EXCESS TSH, TH OR DESICCATED THYROID)
PHYSICAL STATUS		
Appearance	Lethargic, bloated	Apprehensive 'frightened look
Age	Any	Any
Mental response	Poor, slow	Quick, alert
Weight	Variable	Evidence of emaciation may be severe
Integument		
Texture	Scaling, wrinkled, rough	Smooth, delicate
Temperature	Cool	Warm
Moisture	Dry	Excessive
Nails	Brittle, thick	Fissures, undergrooved
Hair		
Head	Dry, brittle, often fine, falls out easily	Normal
Sexual	Normal, scant or absent	Normal or decreased
Eyes		
General	Puffiness of lids, watery	Normal stare or exoph thalmos
Palpebral fissures	Narrow	Wide
Muscles	Normal	Paralyses may occur
Voice	Hoarse, deep	Normal
Speech	Slow, deliberate	Quick, talkative
Thyroid gland	Not palpable usually	Enlarged in majority
Heart		
Rate	Bradycardia	Tachycardia
Output	Decreased	Increased
Tonus	Decreased	Decreased
Irritability	Decreased	Increased
Circulation		
Peripheral	Decreased	Increased
Time	Increased	Decreased
Blood		
Pressure	Decreased	Increased
Flow	Decreased	Increased
Volume	Decreased	Increased
Movements	Slow, awkward	Hasty, restless
Bone		
Growth (in young)	Retarded	Accelerated
Density	Increased	Decreased
Maturation	Decreased	Increased
Muscles	Normal	Normal or atrophy

**HYPOSECRETION
(PRIMARY THYROID
DEFICIENCY, NOT
FROM ABSENT TSH)**

**HYPERSECRETION
(FROM EXCESS TSH
TH, OR DESICCATED
THYROID)**

LABORATORY DATA

Alimentary tolerance for glucose	Increased	Decreased
Absorption through gastro intestinal tract (probably all substances capable of absorption)	Decreased	Increased
Adrenalin response	Decreased	Increased
Androgens (17 ketosteroids)	Decreased	Normal and decreased
Basal metabolic rate	Decreased	Increased
Calcium		
Bone	Increased	Decreased
Fecal	Decreased	Increased
Serum	Normal	Normal
Urinary	Decreased	Increased
Cholesterol		
Esters	Increased	Decreased
Destruction	Increased	Decreased
Free	Increased	Decreased
Creatine		
Blood	Decreased	Normal or increased
Dietary	Decreased	Increased
Urinary	Decreased	Increased
Tolerance	Increased	Decreased
Estrogens	Normal	Normal
FSH (urinary follicle stimulating hor- mone)	Negative, occasionally positive	Negative, occasionally positive
Glycogen		
Glycogenolysis	Decreased	Increased
Liver	Increased	Decreased
Hematology		
Hemoglobin	Normal or decreased	Normal or decreased
Red blood cells	Normal or decreased	Normal (rarely increased or decreased)
White blood cells	Normal or decreased	Variable
Iodine		
Inorganic	Decreased	Increased
Organic	Decreased	Increased
Total	Decreased	Increased
Urinary	Decreased	Increased
Insulin sensitivity	Decreased	Increased
Lipids (blood)	Increased	Decreased
Nitrogen		
Excretion	Decreased	Increased
Retention	Increased	Decreased

	HYPOSECRETION (PRIMARY THYROID DEFICIENCY NOT FROM ABSENT TSH)	HYPERSCRETION (FROM EXCESS TSH, TH OR DESICCATED THYROID)
Protein		
Total serum	Normal or increased	Normal or decreased
Albumin	Normal or decreased	Decreased
Globulin	Normal or decreased	Normal or increased
Spinal fluid	Increased	Decreased
Phosphatase (alkaline growth phase)	Decreased	Increased
Phosphorus		
Blood	Normal or decreased	Normal or increased
Urinary	Decreased	Increased
TSH (urinary thyrotropic hormone—see Chart 30)		
Active	Increased	Decreased or absent
Inactive	Absent	Increased
Specific dynamic action of protein	Decreased (or absent)	Variable
Sugar		
Blood	Normal or decreased	Variable
Tolerance	Increased	Variable
Urinary	Absent	Absent or increased
Urea (blood)	Decreased	Increased
Water		
Excretion	Decreased	Increased
Retention	Increased	Decreased
SYMPTOMATOLOGY		
Neuromuscular and sensory		
Fatigue	Usual	Marked
Heat	Tolerance	Intolerance
Memory	Poor	Alert
Nervousness	None	Marked
Sleepiness	Common	None
Sweating	None	Marked
Tremor	None	Present
Cardiovascular		
Angina of effort	May occur	May occur
Dyspnea	May be present	Often present
Palpitation	None	Common
Gastro intestinal		
Appetite	Anorexia	Polyphagia
Bowel movements	Normal or constipation	Normal or diarrhea
Weight	Gain	Loss
Genito urinary		
Menses	Amenorrhea or menorrhagia	Normal, amenorrhea or oligomenorrhea

XIII EXAMINATION OF PATIENT**A HISTORY****1 Abnormal function**

- a Diagnosis of hypersecretion or hyposecretion can often be made from the history alone
- b Hyposecretion
 - (1) Sluggishness
 - (2) Somnolence
 - (3) Sensitivity to cold
 - (4) Dryness of skin
 - (5) Weight gain in some
 - (6) Growth retardation (children)
- c Hypersecretion
 - (1) Weight loss with adequate food intake
 - (2) Palpitation
 - (3) Sensation of warmth
 - (4) Tremor
 - (5) Nervousness
 - (6) Sweating

2 Tracheal compression

- a Dyspnea associated with stridor
- b Development may be
 - (1) Gradual
 - (2) Sudden (hemorrhage into goiter)

3 Malignancy

- a Thyroid gland may grow rapidly
- b Pressure symptoms
- c History of comparatively little value

4 Thyroiditis

- a Acute febrile state
- b Thyroid
 - (1) Tenderness
 - (2) Swelling
 - (3) Pain (present or past) is often noted on swallowing

B PHYSICAL STATUS**1 Appearance and behavior**

- a Myxedema
 - (1) Facial expression dull
 - (2) Bloated appearance often
 - (3) Speech slow
 - (4) Behavior sluggish
- b Hyperthyroidism
 - (1) Restless
 - (2) Alert
 - (3) Nervous
 - (4) Frightened ("frozen fright")

2 Eye signs

- a Myxedema
 - (1) Gaze impassive

- (2) Puffiness, transparent edema below and lateral to lids in some cases

- (3) Palpebral fissures narrow

b Hyperthyroidism

- (1) Stare
- (2) Exophthalmos
- (3) Lid retraction
- (4) Lack of convergence
- (5) Ocular palsy or palsies
- (6) Puffiness

3 The thyroid gland**a Inspection for**

- (1) Enlargement
 - (a) Unilateral
 - (b) Bilateral
- (2) Contours
 - (a) Uniform
 - (b) Nodular
 - (c) Irregular
- (3) Location
- (4) Veins of neck and/or chest and abdomen which may show
 - (a) Distention
 - (b) Pulsations
 - (c) Tortuosities
- (5) Other lumps in the neck
 - (a) Lymph glands
 - (b) Lateral aberrant tissue
 - (c) Thyroglossal cyst
 - (d) Branchial cyst

b Palpation (see Fig 121)**(1) Method**

- (a) Left sternocleidomastoid muscle is relaxed by turning the head to right or vice versa
- (b) Displace the thyroid cartilage with the thumb from left side
- (c) Thumb and middle finger of other hand firmly grasp thyroid lobe on the right side
- (d) Patient swallows

(2) Examination for

- (a) Tenderness
- (b) Consistency
 - [1] Firm
 - [2] Soft
 - [3] Hard
 - [4] Smooth
 - [5] Nodular

- [6] Irregular
 - [7] Pebbly
 - (c) Size—each normal lobe (average)
 - [1] Length— $1\frac{1}{2}$ in
 - [2] Thickness— $\frac{1}{2}$ in
 - (d) Location
 - [1] Normal
 - [2] Substernal
 - [3] Intrathoracic
 - [4] Aberrant
 - (e) Fixation to surrounding structures
 - (f) Other lumps in neck
 - (g) Tracheal displacement by goiter—laryngeal prominence of thyroid cartilage should be in midline normally
 - (h) Thrills which may be present
 - c Auscultation—bruits may be heard
 - d Stridor (see Fig 122)
 - (1) Present in some with abnormal position of head
 - (2) Anterior compression may be demonstrated with forward flexion of the head
 - (3) Lateral compression may be found when head is bent or turned to either side
 - e Measurement of size—neck circumference may be used as an index but
 - (1) Difficult to determine accurately
 - (2) Unreliable for minor changes
 - f Transillumination—cystic nature of thyroid nodules may be revealed
 - 4 Vocal cord examination—this should be done for possible laryngeal nerve paralysis
 - 5 Neuromuscular system in hyperthyroidism
 - a Tremor—fine type of
 - (1) Extremities
 - (2) Whole body occasionally
 - b Quadriceps weakness
 - (1) Leg test (Lahey)¹¹
 - (a) Method
 - [1] Patient sits forward on edge of chair
 - [2] His arms are dropped to the sides, and his hands should be free
 - [3] One leg is then raised parallel with the floor
 - [4] An attempt is made to hold it for 1 min
 - (b) Results
 - [1] Negative
 - [a] Normal person has little difficulty in keeping leg in this position for 1 min
 - [b] Some patients give up shortly and voluntarily drop the leg especially nervous individuals without hyperthyroidism
 - [2] Positive
 - [a] Patient cannot prevent a gradual lowering of his leg
 - [b] Tremor usually increases as his leg slowly sinks to the floor
- (2) Chair test (Plummer)
 - (a) Method
 - [1] Patient puts one foot on seat of a low chair
 - [2] He tries to raise himself onto it
 - (b) Results
 - [1] Negative—easily performed
 - [2] Positive—patient cannot accomplish this without using his arms in pulling himself up
- 6 Cardiovascular system
 - a Pulse
 - (1) Myxedema
 - (a) Bradycardia
 - (b) Normal
 - (2) Hyperthyroidism
 - (a) Tachycardia usually
 - (b) Irregular (10%)
 - (c) Forceful or bounding with rapid collapse in diastole
 - b Blood pressure
 - (1) Myxedema
 - (a) Variable
 - (b) Nothing characteristic

(2) Hyperthyroidism

(a) Pulse pressure of 60 mm or more

(b) Diastolic pressure usually below 80 mm (unless coexistent hypertension)

(c) Diastolic pressure may be read as zero, simulating a true Corrigan pulse of aortic insufficiency

[1] To distinguish between the two, the stethoscope is placed so that the distal rim of the diaphragm is pressed firmly against the artery (method of Blumgart)⁴

[2] Higher level of diastolic pressure will then be found unless aortic insufficiency is also present

bolic rate below minus 20 per cent

[2] Association with a low basal metabolic rate increases the possibility of the diagnosis but may be found in apparently normal individuals

(b) Upper normal values do not eliminate either one⁴

(c) Clinical evidence is important, but if lacking a therapeutic trial of desiccated thyroid may be worthwhile (see 25 XVI C)

(2) Hypersecretory diffuse hyperplastic thyroid

(a) Low levels which are proportional to the basal metabolic rate elevation is less striking than the reverse relationship in myxedema

(b) Usefulness in diagnosis is limited

(c) Trend during treatment may be of some value

(3) Hypercholesterolemia—other causes

(a) Of 404 individuals suspected of having a high plasma cholesterol for various reasons (including thyroid deficiency) 65 per cent had thyroid deficiency⁷

(b) Therefore the probable chance of a high cholesterol indicating thyroid deficiency regardless of clinical findings, is 2 in 5

d Diagnostic response to treatment

(1) Myxedema

(a) Desiccated thyroid administration (not over 2 gr per day) produces a striking fall (usually 50%)

(b) Marked drop with cholesterol free diet but adequate in calories without thyroid treatment

(2) Hyperthyroidism—reciprocal rise in majority of cases with fall in basal metabolic rate

(3) Hypercholesterolemia—other causes

C LABORATORY DATA

1 Cholesterol (plasma or serum)

2 Iodine

a Urine

b Blood

3 Basal metabolic rate

4 Urinary thyrotropic hormone—analysis impractical for routine use

D METHODS FOR SPECIAL PROCEDURES

1 Cholesterol (serum or plasma)² (see 103 III Charts 31 and 32)

a Fasting state unnecessary for collection of blood samples

b Average values

(1) Normal MG % 180

(a) Children have lower values

(b) Older age groups show higher levels

(2) Myxedema 300

(3) Hyperthyroidism 140

(4) Panhypopituitarism 200

(5) Hypometabolism 180

c Interpretation

(1) Myxedema and cretinism

(a) High readings

[1] Result of thyroid deficiency (other causes excluded) more often than is a basal meta

- (1) More resistant to desiccated thyroid medication
 - (b) Cholesterol free diet is not as effective in producing a decrease
- 2 Iodine (see 103 IX)
- a Urinary (see 26 XI 10 Table 13 34 IX 4 103 IX)
 - (1) Excretion has clinical significance chiefly in detection of factitious hyperthyroidism
 - (2) Same precautions as for collection of blood for total iodine
 - (3) Results over 800 to 1 000 micrograms/24 hrs indicate ingestion of desiccated thyroid (or iodine)
 - b Blood (see Chart 33)
 - (1) Comment
 - (a) Total blood iodine is a fair index of circulating thyroid hormone when collected under certain strict precautions since it is subject to easy change from
 - [1] Diet
 - [2] Medication
 - [3] Contamination
 - (b) Protein bound iodine is the best chemical measure of thyroid hormone in the blood and is little affected by diet or contamination but may be by ingestion of large quantities of iodine preparations¹³
 - (2) Interpretation
 - (a) Total blood iodine—in absence of factors other than excess thyroid hormone a high level = corroborative evidence of hyperthyroidism
 - (b) Protein bound iodine
 - [1] Borderline values are of little diagnostic significance
 - [2] Increased values usually indicate hyperthyroidism except in pregnancy
 - [3] Normal (or almost) levels are possible as for total iodine in severe and long standing hyperthyroidism
- 3 Basal metabolic rate
- a Preparation of patient
 - (1) No food 12 hrs preceding test
 - (2) Sips of water may be allowed
 - (3) A comfortable night's sleep is desirable, sedatives are indicated for restlessness
 - (4) Emotional disturbances must be avoided preceding test, otherwise test should be postponed
 - (5) Check temperature, defer procedure if elevated
 - b Place of test
 - (1) Overnight stay at place of test desirable results run 10 per cent lower under these circumstances
 - (2) If above not possible travel to place of test should be with least possible effort
 - (3) Patient should rest in reclining position at least 20 to 30 min before procedure
 - (4) Surroundings should be
 - (a) Quiet
 - (b) Restful
 - c Technician qualifications of
 - (1) Accuracy
 - (2) Poise
 - (3) Tact
 - (4) Kindness
 - (5) Patience
 - d Important technical points
 - (1) Replace soda lime frequently
 - (2) Check apparatus for leaks
 - (3) Adjust nose clip comfortably
 - (4) Do not remove false teeth
 - (5) Be suspicious if
 - (a) Pulse rate is low
 - (b) Oxygen consumption appears rapid
 - (6) Recalculate all tests for confirmation
 - e Interpretation
 - (1) Normal test
 - (a) The concept of what constitutes this is somewhat in definite, although minus 15 per cent to plus 5 per cent = average
 - (b) The metabolic trend on repeated tests on subsequent days is more reliable because of

- [1] Unfamiliarity with procedure
- [2] Apprehension
- (2) Myxedema
 - (a) A low level (minus 20% or below) is usual⁷⁻⁹
 - (b) Occurrence only 2 out of 5 people with readings of minus 20 per cent or lower
- (3) Hypersecretory hyperplastic gland (untreated)
 - (a) Results of plus 20 per cent or over are commonest
 - (b) Rare exceptions when an individual's normal rate is low (about minus 20% or below) before onset of the disease, then the readings may be only plus 5 per cent or so
 - (c) A high rate is not diagnostic per se, because evidence of the disorder must also be present
- f High readings, exclusive of hypersecretory nodular or hyperplastic thyroids⁶
 - (1) Factitious hyperthyroidism
 - (2) Acromegaly
 - (3) Cushing's syndrome
 - (4) Pheochromocytoma
 - (5) Diabetes mellitus (in acidosis)
 - (6) Blood dyscrasias
 - (a) Leukemia (lymphatic or myelogenous)
 - (b) Polycythemia vera
 - (c) Pernicious anemia
 - (d) Splenic anemia
 - (7) Aortic stenosis⁹⁻¹⁰⁻¹¹
 - (8) Congestive heart failure
 - (9) Malignant or severe hypertension
 - (10) Pregnancy (last few weeks and during lactation)
 - (11) Fever
 - (12) Certain individuals never can adapt themselves to this test so trial of oral sedation to point of drowsiness is indicated
- g Low readings, exclusive of myxedema⁶
 - (1) Normal
 - (2) Panhypopituitarism
 - (3) Adrenal insufficiency
 - (4) Hypogonadism
 - (5) Prolonged inactivity, i.e., bed ridden patients
 - (6) Chronic malnutrition from any cause
 - (7) Anorexia nervosa
 - (8) Psychotic states or variety of diseases of nervous system, i.e.
 - (a) Severe mental depression
 - (b) Schizophrenia
 - (c) Psychoneurosis
 - (9) Amputation of extremities
 - (10) Nephrotic syndrome
 - (11) Idiopathic
 - (12) Miscellaneous

TABLE 14 HYPOMETABOLISM (BMR—12% OR BELOW) IN 308 CASES⁹

CAUSE	PER CENT
Idiopathic	33.0
Clinical myxedema (usually below minus 25%)	6.1
Miscellaneous	60.9

- 4 Basal metabolism test under pentothal anesthesia (see Chart 34)
 - a Indications
 - (1) Elevated basal metabolic rate without evidence of hyperthyroidism
 - (2) Determination of true basal metabolic rate in hyperthyroidism when associated with other causes for an elevated reading (see below)
 - b Method
 - (1) Trained anesthetist should prepare patient
 - (2) Atropine sulfate gr 1/150 subcutaneously, 1 hr before procedure
 - (3) Throat sprayed with 10 per cent cocaine solution a few minutes before test
 - (4) Sodium pentothal solution injected intravenously using small amount to produce complete relaxation
 - (5) Rubber mouthpiece inserted if breathing is unhampered

- (6) Metal airway attached to rubber mouthpiece whenever breathing is not free
- (7) Adhesive tape applied around rubber mouthpiece and mouth to prevent leakage of air
- (8) Chin supported to facilitate breathing
- (9) Additional pentothal given if needed, hyperthyroid patients require larger doses than others
- e Interpretation
 - (1) Elevated readings
 - (a) Hyperthyroidism—all types
 - (b) Acromegaly
 - (c) Pheochromocytoma
 - (d) Aortic stenosis
 - (2) Normal in
 - (a) Parkinson's disease
 - (b) Spasmodic torticollis
 - (c) Nervous states
 - (d) Hypertension
- 5 Thyrotropic hormone assays (see 14 VIII)
 - a Comment
 - (1) Extremely difficult procedure
 - (2) Limited clinical value
 - (3) Inactivated hormone is reactuated by reducing agents
 - b Normal
 - (1) Urine—about 2 Junkmann Schoeller units per day¹²
 - (2) Blood—negative or 0.005 to

0.0025 Junkmann Schoeller units (results depend on the type of test)³

- c Hypothyroidism (urine and blood)
 - (1) Active—positive
 - (2) Inactive—absent
- d Hyperthyroidism (urine and blood)
 - (1) Active—absent
 - (2) Inactive—present

E. ROENTGENOGRAMS AND FLUOROSCOPY

- 1 Trachea (using Bucky diaphragm)
 - a Views
 - (1) Anteroposterior
 - (2) Oblique
 - (3) Lateral
 - b Indication—to determine degree of tracheal compression
- 2 Esophagus for involvement by extension of thyroid malignancy
- 3 Chest
 - a Substernal or mediastinal shadow
 - b Movement of substernal mass on swallowing
 - c Tracheal deviation
 - d Metastatic lesions
 - e Motion of diaphragm
 - f Congestive failure
 - g Heart
 - (1) Size
 - (2) Contour
 - (3) Contractions
 - (4) Rate
 - (5) Rhythm

REFERENCES

I HISTORY

- 1 Abbé R. Exophthalmic goitre reduced by radium. *Arch Roentg Ray* London 9 214 218 1904 1905
- 2 Abelin J. Einfluss des Dijodtyrosins auf den hyperthyreotischen Stoffwechsel. *Biochem Zeitschr* 233 483-485 1931
- 3 Allen B M. The results of thyroid removal in the larvae of *Rana pipiens*. *J Exper Zool* 24 499 517 (Jan) 1917 1918
- 4 Aron M. Action combinée de la thyroxine et de l'extrait préhypophysaire sur la thyroïde chez le cobaye. *Compt rend Soc de biol* 104 96 98 (May) 1930
- 5 Aron M and Benoit J. Action antagoniste de la thyroïdine préhypophysaire et de la folliculine ovarienne sur le fonctionnement thyroïdien. *Compt rend Soc de biol* 109 923 925 (Apr) 1931
- 6 Astwood E B. Treatment of hyperthyroidism with thiourea and thiouracil. *J.A.M.A.* 122 78 81 (May) 1943
- 7 Baber M C. Contributions to the minute anatomy of the thyroid gland of the dog. *Phil Tr* London 166 557 563 1877
- 8 Ballet G and Enriquez E. Des effets de l'hyperthyroïdisation expérimentelle. *Méd mod.* Paris 801 804 1895
- 9 Baumann E. Ueber das normale Vorkommen von Jod im Thierkörper. *Zeitschr f physiol. Chem* 21 319 330 1895
- 10 Beclere A. Un nouveau cas de myxœdème guéri par l'alimentation thyroïdienne. Le thyroïdisme dans ses rapports avec la maladie de Basedow. Avec l'hystérie. *Bull et mém Soc méd d hop de Paris 3e série* 11 631 646 (Oct) 1894
- 11 Begbie J. Anemia and its consequences: enlargement of the thyroid gland and eyeballs. Anemia and goitre: are they related? *Month J M Sc* 9 495 508 (Feb) 1849
- 12 Bernays A C. The origin of the foramen caecum linguae as shown by an operation on a rare tumor of the root of the tongue: a preliminary note. *St Louis M J* 55 201 205 1883

- 13 Bettencourt R and Serrano J A *Congrès de Limoges II Section des sciences médicales Progres med* 12 1:0 1890
- 14 Blizard W Observations in the Surgical Anatomy of the Head and Neck, Edinburgh Bryce 1811 p 202
- 15 Blumgart H L Levine M A and Berlin D Congestive heart failure and angina pectoris the therapeutic effect of thyroidectomy in patients without clinical or pathological evidence of thyroid toxicity *Arch Int Med* 51 866 877 (June) 1933
- 16 Bri saud N De l'infantilisme myxoedémateux *Nouv icon de la Salpêtr Paris* 10 240 267 1897
- 17 Burns A Observations on the Surgical Anatomy of the Head and Neck. Edinburgh Bryce 1811 p 202
- 18 Cannon W H Binger C A L and Fitz R Experimental hyperthyroidism *Am J Physiol* 36 363 364 (Mar) 1915
- 19 Cheadle W M Exophthalmic goiter *St Georges Hospital Reports* 4 175 192 1869
- 20 Chesney A M Clawson T A and Webster B Endemic goitre in rabbits *Bull Johns Hopkins Hosp* 43 261 277 (Nov) 1928
- 21 Cohnheim J Einfacher Gallertkropf mit Metasta in Virchow's Arch 68 547 559 1876
- 22 Coindet J F Découverte d'un nouveau remède contre le goitre *Ann de chim et phys* 15 49 59 1810
- 23 Columbus Realdus quoted by Rolleston H H *The Endocrine Organs in Health and Disease* London Oxford 1936 p 145
- 24 Cooper A O P The Anatomy of Thyms Gland London Longman Rees Orme Green & Brown 1832 pp 44-47
- 25 Cooper A Notes on the structure of the thyroid gland *Guys Hosp Rep* 1 443 456 1836
- 26 Cope O Rawson R W and McArthur J W Hyperfunctioning single adenoma of thyroid *Surg Gynec & Obst* 84 415-426 (Apr) 1947
- 27 Courtois B Découverte d'une substance nouvelle dans le vareck *Ann chim Paris* 88 304 310 1813
- 28 Craver L F Cancer of thyroid and its present day treatment embodying experience of Memorial Hospital of New York *Ann Surg* 112 833 853 (Dec) 1925
- 29 Curling T B Two cases of absence of the thyroid body *Med Chir Tr London* 33 303 306 1850
- 30 Dalrymple John quoted by Cooper W W On protrusion of the eyes in connexion with an anaemia palpitation and goitre *Lancet* 1 551 556 (May) 1849
- 31 Demarres M Maladies des yeux *Paris Gazette des Hôpitaux Jan* 1853 pp 2 3
- 32 de Saint Yves Nouveau traite des maladies des yeux *Paris* 1722 pp 141 146
- 33 Drouet P L Le rôle de l'hypophyse dans l'hyperthyroïdie et le syndrome para basedowien contribution à l'étude de l'hyperpituitarisme *Rev frse d'endocrinol* 12 101 136 (Apr) 1934
- 34 Dunhill T P Remarks on partial thyroidectomy with special reference to exophthalmic goitre and observations on 113 operations under local anaesthesia *Brit M J* 1 1222 1225 (May) 1909
- 35 Elmer A W and Scheps M The iodine content of blood and of urine and the basal metabolic rate their value in the diagnosis of the function of the thyroid gland *Acta med Scandinav* 116 126 136 1934
- 36 Étienne H and Drouet P L Le traitement de la maladie de Basedow en fonction de l'intervention de l'hypophyse dans l'hyperthyroïdie, *Bull Acad de med Paris* 112 86 95 (July) 1934
- 37 Fagge C H On poradic cretinism occurring in England *Med Chir Tr London* 54 115 1871
- 38 Fallopio G De tumoribus praeter naturam *Venetiae* 1563
- 39 Flajani G Collezione d'osservazioni e riflessioni di chirurgia *Rome* 3 2 0 1907
- 40 Fodéré F M Traite du goitre et du cretinisme, Paris 1800
- 41 For E L A case of myxoedema treated by taking extract of thyroid by the mouth *Brit M J* 2 941 (Oct) 1892
- 42 Gilen quoted by Hertz J On Goitre and Allied Diseases Copenhagen Munksgaard and London Oxford 1943 p 12
- 43 Gifford H A new eye symptom in Grave disease *Ophth Rec* 15 249 255 1906
- 44 Goetsch S Newer methods in the diagnosis of thyroid disorders pathological and clinical *New York State J Med* 18 259 267 (July) 1918
- 45 Graves R J Newly observed affection of the thyroid gland in females its connexion with palpitation—with fits of hysteria *London M & S J* 7 (pt 2) 316 317 1835
- 46 Greenfield W S Some diseases of the thyroid gland *Lancet* 2 1493 1497 1533 1553 (Dec) 1893
- 47 Griesbach W E and Purves H D Studies on experimental goitre V Pituitary function in relation to goitrogenesis and thyroidectomy *Brit J Exper Path* 24 174 184 (Oct) 1943
- 48 Gudernatch J F Feeding experiments on tadpoles II A further contribution to the knowledge of organs with internal secretion *Am J Anat* 15 431 480 (Jan) 1914
- 49 Gull W W On a cretinoid state supervening in adult life in women *Tr Clin Soc* 7 180-185 1874
- 50 Haller A quoted by DeCoursy J L and DeCoursy C B Pathology and Surgery of Thyroid Disease p 42 Springfield Ill Thomas 1949
- 51 Halsted W S The significance of the thymus in Graves disease report of two cases of resection of the thymus gland *Tr Am S A* 32 287 321 1914
- 52 — The results of the x ray treatment of the thymus gland in Graves disease *Bull Johns Hopkins Ho* p 26 55 (Feb) 1915
- 53 Hamilton J G Rates of absorption of radio active sodium potassium chlorine bromine and iodine in normal human subjects *Am J Physiol* 124 667 678 (Dec) 1938
- 54 Hamilton J G and Lawrence J H Recent clinical developments in the therapeutic application of radio phosphorus and radio iodine *J Clin Investigation* 21 624 (May) 1942
- 55 Hamilton J G and Soley M H Studies in iodine metabolism by the use of a new radio active isotope of iodine *Am J Physiol* 127 557 572 (Oct) 1939
- 56 Hamilton J G Soley M H and Eichorn, A B Deposition of radioactive iodine in

- human thyroid tissue Univ California Publ Pharmacol 1 339 367 1940
- 57 Harrington C R Chemistry of thyroxine isolation of thyroxine from thyroid gland Biochem J 20 293 299 1976
 - 58 Harrington C R and Harger G Chemistry of thyroxine constitution and synthesis of thyroxine Biochem J 21 169 181 1927
 - 59 Harrington C R and Randall S S Observations on iodine-containing compounds of thyroid gland isolation of diiodotyrosine Biochem J 23 373-383 1929
 - 60 Harrington C R and Salter W T The isolation of thyroxine from the thyroid gland by the action of proteolytic enzymes Biochem J 24 456 471 1930
 - 61 Hashimoto H Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma Lymphomatosa) Arch f klin Chir 97 219 248 1912
 - 62 Hedenus A G Tractatus de glandula thyroidea tam sana quam morboza imprimis de struma eiusque causis atque medela Lipsia 1822 pp 219 300
 - 63 Hertoghe E Thyroid deficiency Med Rec 86 489 505 1914
 - 64 Hertz S and Roberts A Application of radio active iodine therapy of Graves disease J Clin Investigation 21 624 (Sept) 1942
 - 65 Hertz S Roberts H and Evans R D Radio active iodine as indicator in study of thyroid physiology Proc Soc Exper Biol & Med 38 510 513 (May) 1935
 - 66 His Wilhelm Sr Anatomie menschlicher Embryonen I Embryonen des ersten Monats Leipzig Vogel 1880
 - 67 Hoeler W Hercules medicus sive locorum communium medicorum tomus unicus p 43 Viennae 1657
 - 68 Horsley V A A recent specimen of artificial myxoedema in a monkey Lancet 2 827 1834
 - 69 Hoskins E H and Hoskins M M Further experiments with thyroidectomy in amphibia Proc Soc Exper Biol & Med 15 102 104 (Apr) 1918
 - 70 Hunt R Influence of thyroid feeding upon poisoning by acetonitrile J Biol Chem 1 33 44 1905
 - 71 Hunt R and Seidel A Studies on thyroid I Relation of iodine to the physiological activity of thyroid preparations Bull 47 Hrg Lab U S Pub Health and MHS 1908
 - 72 Joffroy A Nature et traitement du goitre exophtalmique Progres med 18 477 480 (Dc) 1893
 - 73 Kendall E C The isolation in crystalline form of the compound containing iodine which occurs in the thyroid its chemical nature and physiological activity JAMA 64 2042 2043 (June) 1915
 - 74 Keston A Ball R P Frantz V K and Palmer W W Storage of radioactive iodine in metastasis from thyroid carcinoma Science 95 362 363 (Apr) 1942
 - 75 King T W Observations on the thyroid gland Guy's Hosp Rep 1 429-437 1836
 - 76 Kocher E T Zur Pathologie und Therapie des Kropfes Deutsche Zeitschr f Chir 11 191 229 1878
 - 77 ——— Ueber Kropfexstirpationen und ihre Folgen Arch f klin Chir 29 254 337 1883
 - 78 ——— Chirurgische Operationslehre Jena 1907
 - 79 ——— Blutuntersuchungen bei Morbus Basedown mit Beiträgen zur Frühdiagnose und Theorie der Krankheit Arch f klin Chir 87 131 157 1908
 - 80 Lahey F H and Hamilton B E Thyrocarcinomas their diagnostic difficulties their surgical treatment Surg Gynec & Obst 39 10 14 (July) 1924
 - 81 Lannelongue Der erste Versuch eine Thierschilddrüse auf den Menschen zu überpflanzen Wien med Bl 13 195 196 (Mar) 1890
 - 82 Langl C De glandula thyroidea in cavum usque thoracis sub sternum sese expandente casus singularis Monachi Poessenbacher 1830
 - 83 Loeb L Compensatory hypertrophy of thyroid gland J M Research 42 77 (July Sept) 1920
 - 84 Loeb L and Friedman H Long continued injections of acid extract of anterior pituitary on thyroid gland and sex organs Proc Soc Exper Biol & Med 29 172 174 (Nov) 1931
 - 85 Luden G Studies in cholesterol V Blood cholesterol in malignant disease and effect of radium on blood cholesterol Collected Papers Mayo Clinic Philadelphia Saunders 1918 Vol 10 p 470
 - 86 MacCallum W G and Cornell W H On the mechanism of exophthalmos M News 85 732 736 1904
 - 87 Mackenzie H W G A case of myxoedema treated with great benefit by feeding with fresh thyroid gland Brit M J 2 940 941 (Oct) 1892
 - 88 Mackenzie J M Mackenzie C G and McCollum E Effect of sulfinylguanidine on thyroid of rat Science 94 518 519 (Nov) 1941
 - 89 Magnus Levy A Ueber den respiratorischen Gewebsel unter dem Einfluss der Thyroiden sowie unter verschiedenen pathologischen Zuständen Berl klin Wchnschr 32 650 652 1895
 - 90 Marie P Sur la nature et sur quelques uns des symptômes de la maladie de Basedow Arch de neur 79 95 1833
 - 91 Marine D and Baumann E J Influence of glands with internal erections on respiratory exchange Am J Physiol 59 353 368 (Feb) 1922
 - 92 Marine D and Kimball G F The prevention of simple goiter in man J Lab & Clin Med 3 40-48 (Oct) 1917
 - 93 Marine D and Rosen S H Exophthalmos in thyroidectomized guinea pigs by thyrotropic substance of anterior pituitary and mechanism involved Proc Soc Exper Biol & Med 30 901 903 (Apr) 1933
 - 94 Marine D Spence A W and Cipra A Production of goiter and exophthalmos in rabbits by administration of cyanide Proc Soc Exper Biol & Med 29 822 823 (Apr) 1932
 - 95 Marine D and Williams W W Relation of iodine to the structure of the thyroid gland Arch Int Med 1 349 384 1908
 - 96 Mason R L Hunt H M and Hursthal L M Blood cholesterol values in hyperthyroidism and myxoedema Their significance New England J Med 203 1273 1278 (Dec) 1930
 - 97 McCarrison R Experimental researches on the etiology of endemic cretinism congenital goitre and congenital parathyroid disease Ind J M Research 1 505 522 1914
 - 98 Meckel J F Manual of General Descriptive

- and Pathological Anatomy Vol 3 p 363 Philadelphia Carey & Lea 1832
- 99 Mobius P J Ueber Insufficienz der Convergenz bei Morbus Basedown Centralbl f Nerven u Psychiat 9 356 358 1886
 - 100 Mori T Ueber das Auftreten thyreotouscher Symptome bei Geschwulstanomalien in der Schilddrüse Frankfurt Ztschr f Path 12 2 24 1913
 - 101 Muller, F Beiträge zur Kenntniss der Basedowschen Krankheit Deutsches Arch f klin Med 51 335 412 (June) 1893
 - 102 Murray G R Note on the treatment of myxoedema by hypodermic injections of an extract of the thyroid gland of a sheep Brit M J 2 796 (Oct.) 1891
 - 103 — Discussion on exophthalmic goiter Brit M J 2 908 914 (Nov.) 1922
 - 104 Muy Johann Neue vernünftige Praxis der Wundarzney Frankfurt 1629 p 345
 - 105 Naffziger H C and Jones O W Jr Surgical treatment of progressive exophthalmos following thyroidectomy J.A.M.A. 99 638 642 (Aug.) 1932
 - 106 Niepce B Traité du goitre et du cretinisme Paris Bailière 1851 1852
 - 107 Ord W M On Myxoedema a term proposed to be applied to an essential condition in the cretinoid affection occasionally observed in middle aged women Med Chir Tr London 61 57 58 1878
 - 108 Oswald A Die Eiweisskörper der Schilddrüse Ztschr f physiol Chem 27 14-49 1899
 - 109 Paracelsus De Generatione Stultorum 1603
 - 110 Pary C H I Enlargement of the thyroid gland in connection with enlargement and palpitation of the heart Collections from Unpublished Medical Writings Vol 2 pp 111 125 London 1825
 - 111 Paulus of Aegineta quoted by Hertz J On Goitre and Allied Diseases Copenhagen Munksgaard and London Oxford 1943 p 15
 - 112 Pinefs F Ueber Thyreoplasia (kongenitales Myxoedem) und infantiles Myxoedem Wien klin Wchnschr 15 1129 1136 (Oct.) 1902
 - 113 Pinsuti quoted by Engelbach W Endocrine Medicine Vol I p 8 Springfield Ill Thomas 1932
 - 114 Plinius quoted by Hertz J On Goitre and Allied Diseases p 11 Copenhagen Munksgaard and London Oxford 1943
 - 115 Plummer H S and Boothby W M The value of iodine in exophthalmic goiter Coll papers Mayo Clinic 15 565 576 1923
 - 116 Prosser T An account and method of cure of the bronchocele or Derbyneck London 1769
 - 117 Prout W Chemistry Meteorology and the Function of Digestion Considered with Reference to Natural Theology p 113 London Wilham Pickering 1834
 - 118 Rehn L Ueber die Exstirpation des Kropfs bei Morbus Basedown Berl klin Wchnschr 21 163 166 (Mar.) 1884
 - 119 Reverdin J L Communication sur les accidents consécutifs à l'ablation totale du goitre Rev méd de la Suisse Rom 2 539 540 1882
 - 120 Riedel B M C L Die chronische zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse Verhandl d deutsch Gesellsch f Chir 25 101 105 (May) 1896
 - 121 Roger of Palermo quoted by Hertz J On Goitre and Allied Diseases p 16 Copenhagen Munksgaard and London Oxford 1943
 - 122 Rienhoff W Jr and Lewis D Relation of hyperthyroidism to benign tumors of the thyroid gland Arch Surg 16 9 116 (Jan) 1913
 - 123 Rogowitsch N Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse Beitr z path Anat u z allg Path 4 453 410 1885-1889
 - 124 Runge M Tumor des Atlas und Epistropheus bei einer Schwangeren Arch f path Anat u Physiol (Virchow's Archives) 66 366 373 1876
 - 125 Savill T D Case of myxoedema Tr Clin Soc London 19 306 308 1836
 - 126 Schiff, E Demonstration of a case with sub-sternal goiter, Deutsche med Zeit 92 1041 (Nov.) 1899
 - 127 Schiff J M Untersuchungen über die Zuckerbildung in der Leber pp 61 62 Würzburg 1859
 - 128 Schockaert J A Enlargement and hyperplasia of thyroids in young duck from injection of anterior pituitary Proc Soc Exper Biol & Med 29 306 308 (Dec.) 1931
 - 129 Schrager V L Lateral aberrant thyroids Surg Gynec & Obst 3 465 475 (Oct.) 1906
 - 130 Shapiro S and Marne D Graves disease with rapid improvement following oral administration of fresh oxyprenal gland Endocrinology 5 699 (Nov.) 1921
 - 131 Sick P Ueber die totale Exstirpation einer kropfig entarteten Schilddrüse und über die Rückwirkung dieser Operation auf die circulationsverhältnisse im Kopfe Med Corr Blatt der Würtemb Ärztliche Verein Stuttgart 199 205 1867
 - 132 Smith N R Extirpation of the thyroid gland, North American Arch M & S Sc 2 309 314 1835
 - 133 Smith P E Effect of hypophysectomy in early embryo upon growth and development of frog Anat Rec 11 57 64 (Oct.) 1916
 - 134 Smith P F and Smith I F Repair and activation of thyroid in hypophysectomized tadpole by parenteral administration of fresh anterior lobe of bovine hypophysis J M Res search 43 267 283 (June July) 1922
 - 135 Stellwag C Ueber gewisse Innervationsstörungen bei der Basedowschen Krankheit, Med Jahrb Wien 17 25 54 1869
 - 136 Trousseau A Exophthalmic Goiter Trousseau's Clinical Lectures Vol 2 p 191 Philadelphia Blakiston 1882
 - 137 Uhlenhuth E and Schwartzbach S S Die Physiologie des Thyreoaktivators bei Amphibien I Beschleunigung der Metamorphose bei den Larven von Salamandern Endokrinologie 15 329 342 1935
 - 138 Ungermann E Über ein Fall von Athyreos und vikarierender Zugenstruma Virch Arch f path Anat 187 58 80 1907
 - 139 Vassale G Intorno agli effetti dell'iniezione in travenosa di succo di tiroide nei cani operati di estirpazione della tiroide Riv sper di frenat Reggio Emilia 16 439 455 1890
 - 140 Vassale G and Generali F Sugli effetti dell'estirpazione delle ghiandole paratiroidee, Riv di pat nerv e ment Firenze 1 95 99 (Feb. Mar.) 1896
 - 141 Vesalius quoted by Hertz J On Goitre and Allied Diseases p 1 Copenhagen Munksgaard and London Oxford 1943

- 142 von Basedow K A Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle *Wchnschr f d ges Heilk Berl* 14 197 204 220 228 (Mar) 1840
- 143 von Bruns P *Struma tuberculosa Beitr z klin Chir* 10 1 12 1893
- 144 von Graefe A Ueber Basedow'sche Deutche *Klin* 116 158 1864
- 145 von Haberer H Ueber die klinische Bedeutung der Thyrustruse mit spezieller Berücksichtigung des Morbus Basedowi und des Status thymicus *Med klin* 10 1087 1093 (June) 1914
- 146 von Hansemann D Schilddrüse und Thymus bei der Basedow'schen Krankheit *Berlin Klin Wchnschr* 42 65 (Jan) 1905
- 147 von Muckulicz J Congress der deutchen Gesellschaft für Chirurgie zu Berlin Die chirurgische Behandlung der Basedow'schen Krankheit *Berlin klin Wchnschr* 32 420 (May) 1895
- 148 von Müller H Anatomische Beiträge zur Ophthalmologie *Arch Ophthal* 4 363 388 1858
- 149 Watson P H Excision of the thyroid gland *Thomas Edinburgh M J* 19 252 255 (Sept) 1874
- 150 Wharton T *Adenographia sive glandularum totius corporis descriptio* p 287 London 1656
- 151 White A and Ciereszko L S Purification of the thyrotropic hormone of the anterior pituitary *J Biol Chem* 140 139 140 1941
- 152 Williams F H *The Roentgen Rays in Medicine and Surgery* ed 2 p 679 New York Macmillan 1903
- 153 Wölfler A Ueber die Entwicklung und den Bau des Kropfes *Arch f klin Chir* 29 1 97 754 866 1883
- 154 Zeckwer I T Davis on L W Keller T H and Livingood C S The pituitary in experimental cretinism *J Structural changes in the pituitaries of thyroidectomized rats* *Am J M Sc* 190 145 157 (Aug) 1935
- 155 Zondek H *Das Myxödem* München med Wchnschr 111 1180 1182 (Oct) 1918

II ANATOMY

- 1 Best C H and Taylor N B *The Physiological Basis of Medical Practice* ed 3 Baltimore Williams & Wilkins 1943 p 1126
- 2 Christopher F A *Textbook of Surgery* Philadelphia Saunders 1945 p 274
- 3 Gray H *Anatomy of the Human Body* ed 23 Philadelphia Lea & Febiger 1936 pp 1257 1260
- 4 Grollman A *Essentials of Endocrinology* Philadelphia Lippincott 1941 p 111
- 5 Means J H *The Thyroid and Its Diseases* Philadelphia Lippincott 1937 p 15
- 6 Nonidez J F Innervation of thyroid gland origin and course of thyroid nerves in dog *Am J Anat* 48 299 329 (July) 1931
- 7 — Innervation of thyroid gland distribution and termination of nerve fibers in dog *Am J Anat* 57 135 169 (July) 1935
- 8 Scammon R H in Abt I A *A Summary of the Anatomy of the Infant and Child* Pediatrics Philadelphia Saunders Vol 1 p 372 1923
- 9 Schaeffer J P Morris *Human Anatomy* ed

10 Philadelphia Blakiston 1942 pp 1491 1493

III EMBRYOLOGY

- 1 Abbott A C and Ball H P Pathology of thyroid gland of human fetus and new born infant *Canad M A J* 24 347 353 (Mar) 1931
- 2 Arey L B *Development of Anatomy* ed 3 p 134 Philadelphia Saunders 1936
- 3 Chapman F M Corner E W Robinson D and D'vans R The collection of radioactive iodine by the human fetal thyroid *J Clin Endocrinol* 8 717 720 (Sept) 1948
- 4 Elmer A W and Scheps M Sur la teneur en thyroxine et en diiodotyrosine de la thyroïde des nouveau nés et des foetus *Compt rend Soc de biol* 118 13/0 1372 1935
- 5 Goldsmith H D Phylogeny of the thyroid descriptive and experimental *Ann New York Acad Sc* 50 281 282 (Jan) 1949
- 6 Keene M F and Hewer E E Glandular activity in human foetus *Lancet* 2 111 112 (July) 1924
- 7 Norris E H Morphogenesis of follicles in thyroid *Am J Anat* 20 411-448 (Nov) 1916
- 8 Palmer W W Leland J P and Gutman A B Microdetermination of thyroxine in thyroid gland of new born *J Biol Chem* 125 615 623 (Oct) 1938
- 9 Salter W T *Endocrine Function of Iodine* p 14 Cambridge Harvard 1940
- 10 Weller H I Jr Development of the thyroid parathyroid and thymus glands in man *Contrib Embryol* 23 93 1932
- 11 Windle W F Physiology of the Fetus Origin and Extent of Function in Prenatal Life p 249 Philadelphia Saunders 1940

IV CONGENITAL ANOMALIES

- 1 Arey L B *Developmental Anatomy* ed 3 p 194 Philadelphia Saunders 1936
- 2 Curling T H Two cases of absence of the thyroid body *Med Chir Tr London* 33 303 306 1850
- 3 DeCoursey J L Intrathoracic goiter *Am J Surg* 64 257 267 (May) 1944
- 4 de Quervain F and Wegelin K Der endemische Kretinismus pp 98 Berlin Springer 1936
- 5 Emge L A Functional and growth characteristics of struma ovarii *Am J Obst & Gynec* 40 738 750 (Nov) 1940
- 6 Erdheim J Ueber Schilddrüsenaplasie II Geschwulste des Ductus thyroglossus III Ueber einige menschliche Kiemenderivate *Beitr z path Anat u z allg Path* 35 366 433 1934
- 7 Frantz V K Forsythe R Hanford J M and Roberts W M Lateral aberrant thyroids *Ann Surg* 115 161 183 (Feb) 1942
- 8 Gusberg E H and Danforth D N Clinical significance of struma ovarii *Am J Obst & Gynec* 48 537 542 (Oct) 1944
- 9 Lahey F H Diagnosis and management of intrathoracic goiters *JAMA* 75 163 166 (July) 1920
- 10 — Tumors of the neck *S Clin North Amer* 19 27 486 500 (June) 1947
- 11 MacCallum W H and Fabyan M On the anatomy of a myxoedematous idiot *Bull Johns Hopkins Hosp* 11 341 345 (Sept) 1907

- 12 Maresch R Congenital Defect der Schilddrüse bei einem 11 jährigen Mädchen mit vorhandenen Epithelkörperchen *Ztschr f Heilk* 19 249 269 1893
 - 13 Miller M H Lingual goitre *New England J Med* 208 480 484 (Mar) 1933
 - 14 Pineles F Ueber Thyreoplasia (kongenitales Myxoedem) und infantiles Myxoedem *Wien klin Wchnschr* 15 1129 1136 (Oct) 1907
 - 15 Plaut A Ovarian struma a morphologic pharmacologic and biologic examination *Am J Obst & Gynec* 25 351 360 (Mar) 1933
 - 16 Shapiro P F Metastasis of thyroid tissue to abdominal organs with special case report of struma ovarii metastasizing to omentum *Ann Surg* 92 1031 1042 (Dec) 1930
 - 17 Ulrich H F Lingual thyroid *Ann Surg* 95 503 507 (Apr) 1932
 - 18 Warren S and Feldman J D The nature of lateral aberrant thyroid tumors *Surg Gynec & Obst* 81 44 (Jan) 1949
 - 19 Wynne H M N McCartney J S and McClelland J F Struma ovarii *Am J Obst & Gynec* 39 263 269 (Feb) 1940
- ## V HISTOLOGY
- 1 Blum F and Grutznher R Studien zur Physiologie der Schilddrüse VI Jodpeicherung und Jodbindung im Organismus *Ztschr f physiol Chem* 92 360 382 1914
 - 2 Bremer J L A Textbook of Histology ed 5 pp 344 348 Philadelphia Blakiston 1936
 - 3 Cowdry E V A Textbook of Histology ed 2 pp 194 207 Philadelphia Lea & Febiger 1938
 - 4 Cramer W and Ludford R J Cellular activity and cellular structure as studied in thyroid gland *J Physiol* 61 398 408 (June) 1926
 - 5 Dempsey E W Fluorescent and histochemical reactions in the rat thyroid gland at different states of physiological activity *Endocrinology* 34 27 38 (Jan) 1944
 - 6 Dempsey E W and Singer M Observations on the chemical cytology of the thyroid gland at different functional stages *Endocrinology* 38 270 295 (Mar) 1946
 - 7 Dempsey E W The chemical cytology of the thyroid gland *Ann New York Acad Sc* 50 336 357 (Jan) 1949
 - 8 de Robertis E Intracellular colloid of normal and activated thyroid gland of rat studied by freezing drying method *Am J Anat* 68 317 337 (May) 1941
 - 9 — Proteolytic enzyme activity of colloid extracted from single follicles of rat thyroid *Anat Rec* 80 219 231 (June) 1941
 - 10 Gersh I and Caipersson T Total protein and organic iodine in colloid and cells of single follicles of thyroid gland *Anat Rec* 78 303 319 (Nov) 1940
 - 11 Goetsch E Functional significance of mitochondria in toxic thyroid adenomata *Bull Johns Hopkins Ho p* 27 129 133 (May) 1916
 - 12 Krogh M and Okkels H Sur l'histophysiologie du corps thyroïde stades initiaux de la sécrétion thyroïdienne (Abstract) *Compt rend Soc de biol* 112 1694 1696 (May) 1933
 - 13 Maximow A A and Bloom W A Textbook of Histology ed 3 pp 299 30 Philadelphia Saunders 1938
 - 14 Nonidez J F Further observations on para follicular cells of mammalian thyroid *Anat Rec* 53 339 353 (Aug) 1932
 - 15 Okkels H Studies on thyroid gland on histology and cytology of normal and abnormal thyroids in man *Acta path et microbiol Scand* 9 1 20 1932
 - 16 Okkels H Stades initiaux de la sécrétion thyroïdienne les granulations oxydiques *Compt rend Soc de biol* 116 251 254 1934
 - 17 Severinhaus A F Cytological observations on secretion in normal and activated thyroids *Ztschr f Zellforsch u mikr Anat* 19 653 680 1933
- ## VI FUNCTIONS
- ### II Thyroid Hormone
- 1 Abelin I and Spichtin W Über den Einfluss der Schilddrüsen-substanzen auf den Gesamt-kreatinidgehalt der Leber und des Muskels *Biochem Ztschr* 228 250 256 1930
 - 2 Althausen T I A Study of the influence of the thyroid gland in the digestive tract *Tr Am Assn for Study of Goiter* pp 3 40 1939
 - 3 Althausen T I and Stockholm M Influence of thyroid gland on absorption in the digestive tract *Am J Physiol* 123 577 588 (Sept) 1938
 - 4 Bauer J and Feil L Über den Einfluss der Serumlipase durch Thyroxin und de en Hemmung *Ztschr f klin Med* 128 17 89 1934
 - 5 Baumann E J and Hunt L Relation of thyroid secretion to pacific dynamic action *J Biol Chem* 64 709 726 (July) 1919
 - 6 Bodansky M and Duff V B Influence of pregnancy on resistance to thyroxine with data on creatine content of maternal and fetal myocardium *Endocrinology* 20 437 440 (July) 1936
 - 7 — Age as factor in resistance of albino rat to thyroxine with further observations on creatine content of tissues in experimental hyperthyroidism *Endocrinology* 20 541 545 (July) 1936
 - 8 Bodansky M and Pilcher J F Creatine content of heart in experimental cardiac hypertrophy due to hyperthyroidism *Proc Soc Exper Biol & Med* 32 597 598 (Jan) 1935
 - 9 Bodansky M Pilcher J F and Duff V B Concerning relation of environmental temperature to resistance to thyroid and thyroxine and creatine content of heart and other tissues in experimental hyperthyroidism *J Exper Med* 63 523 532 (Apr) 1936
 - 10 Boothby W M Sandiford I Sandiford K and Slosser J The effect of thyroxine on the respiratory and nitrogenous metabolism of normal and myxedematous subjects I A method of studying the reserve or deposit protein with a preliminary report of the results obtained *Tr A Am Physicians* 40 195 195 1935
 - 11 Brett P C Smith J F and Gardner Hill H Carbhydrate tolerance in myxoedema *Quart J Med* 111 327 334 (Apr) 1925
 - 12 Byrom F B The nature of myxoedema *Clin Sc* 1 273 285 (Nov) 1934
 - 13 Cameron A T and Carmichael J Contributions to biochemistry of iodine comparative effects of thyroid and iodine feedin on growth in white rats and in rabbits *J Biol Chem* 45 69 (Dec) 1920
 - 14 — Biochemistry of iodine effect of thyroxine on growth in white rats and in rabbits *J Biol Chem* 46 35 (Mar) 1921

- 15 Coggeshall H C and Greene J A Influence of desiccated thyroid gland thyroxine and inorganic iodine upon storage of glycogen in liver of albino rat under controlled conditions *Am J Physiol* 105 103 109 (July) 1933
 - 16 Coryn E Recherche expérimentale sur l'influence des glandes endocrines sur l'histologie du cartilage de conjugaison *Ann anat path* 16 27 (Jan) 1939
 - 17 Cramer W On the thyroid adrenal apparatus and its function in the heat regulation of the body *J Physiol* 50 xxxviii xxxix (July) 1916
 - 18 Cramer W and Krause R A Carbohydrate metabolism in relation to the thyroid gland and the effect of thyroid feeding on the glycogen content of the liver and on the nitrogen distribution in the urine *Proc Roy Soc London* B 86 550-560 1913
 - 19 Evans H M, Simpson M L and Pencharz R I Relation between the growth promoting effects of the pituitary and the thyroid hormone *Endocrinology* 25 175 182 (Aug) 1939
 - 20 Fleischmann W and Shumacker H B The relationship between serum cholesterol and total body cholesterol in experimental hyper and hypothyroidism *Bull Johns Hopkins Hosp* 71 175 183 (Sept) 1942
 - 21 Gibon J C Jr and Harris A W Clinical studies of the blood volume V. Hypothyroidism and myxedema *J Clin Investigation* 18 59 65 (Jan) 1939
 - 22 Gudernat ch J F Feeding experiments on tadpoles II A further contribution to the knowledge of organs with internal secretion *Am J Anat* 15 431-480 1914
 - 23 Hammett F S Studies of the thyroid apparatus in growth *Am J Physiol* 76 69 (Mar) 1916
 - 24 Hoffmann F, Hoffmann E J and Talesnik J Influence of the thyroid hormone on neuroeffector system of the heart *Am J Physiol* 148 689 699 (Mar) 1947
 - 25 Hurxthal L M Myxedema heart with congestive heart failure and polyserous effusions *New England J Med* 213 264 267 (Aug) 1935
 - 26 Hurxthal L M and Hunt H M Clinical relationships of blood cholesterol with summary of our present knowledge of cholesterol metabolism *Ann Int Med* 9 717 727 (Dec) 1935
 - 27 Kuriyama S Thyroid and carbohydrate metabolism *Am J Physiol* 43 481 495 (July) 1917
 - 28 — Thyroid and liver glycogen *J Biol Chem* 33 193 205 1918
 - 29 Lerman J, Clark R J and Means J H Further observations on the heart in myxedema *Ann Int Med* 8 82 84 (July) 1934
 - 30 Moses L E Mechanism of effect of hyperthyroidism on cardiac glycogen *Am J Physiol* 142 686 699 (Dec) 1944
 - 31 Schneider H A Effects of feeding thyroid substance *Quart Rev Biol* 14 289 310 (Sept) 1939
 - 32 — Effects of feeding thyroid substance *Quart Rev Biol* 14 431 450 (Dec) 1939
 - 33 Stewart H J and Evans W F Peripheral blood flow in myxedema *Arch Int Med* 69 808 821 (May) 1942
 - 34 Thompson W O Studies in blood volume I The blood volume in myxedema with a comparison of plasma volume changes in myxedema and cardiac edema *J Clin Investigation* 2 477 520 (Aug) 1926
 - 35 Uhlenhuth E and Schwartzbach S E Die Physiologie des Thyreoaktivators bei Amphibien I Beschleunigung der Metamorphose bei den Larven von Salamandern *Endokrinologie* 15 329 342 1935
 - 36 Wan, F Clinical and experimental investigation on the creatine metabolism *Acta med Scandinav Suppl* 105 1 338 1939
 - 37 Wilkins L and Fleischmann W Effects of thyroid on creatine metabolism with a discussion of mechanism of storage and excretion of creatine bodies *J Clin Investigation* 25 360 3 7 (May) 1946
 - 38 Zonck H Das Myxodermberg München med Wchnschr 88 1180-1182 (Oct) 1918
- C Thyroidectomy**
- 1 Abram M I and Giligan D R Carbohydrate metabolism in human hypothyroidism induced by total ablation of thyroid gland blood sugar response to insulin *Am J M Sc* 188 796 800 (Dec) 1934
 - 2 Alquier L Sur le modifications de l'hypophyse apres l'extirpation de la thyroïde ou des surrenales chez le chien *J de physiol et de path gen* 9 492 499 1907
 - 3 Altschule M D and Cooper P Changes in pituitary gland following total thyroidectomy *Arch Path* 24 443-453 (Oct) 1937
 - 4 Bensen W Beitrag zur Kenntnis der Organveränderungen nach Schilddrüsen-Extirpation bei Kaninchen *Virchows Arch f path Anat* 170 229 247 (Nov) 1902
 - 5 Bodansky A Effect of thyroidectomy upon the reaction of sheep to insulin *Proc Soc Exper Biol & Med* 21 46 (Oct) 1923
 - 6 Boyce R and Beadles C F A further contribution to the study of the pathology of the hypophysis cerebri *J Path & Bacteriol* 1 359 383 1892 1893
 - 7 Bryant A R Effect of total thyroidectomy on structure of pituitary gland in rabbit *Anat Rec* 47 131 144 (Nov) 1930
 - 8 Chapman A and Higgins G M Role of thyroid in cytologic response of pituitary to low intake of iodine *Endocrinology* 34 83 89 (Feb) 1944
 - 9 Chen G and Van Dyke H B Amount of thyroid stimulating hormone in anterior pituitary of thyroidectomized rabbit *Proc Soc Exper Med & Biol* 32 484 485 (Dec) 1934
 - 10 Chu J P Influence of thyroid gland on pituitary gonadotrophic activity in rabbit *Endocrinology* 34 90 10 (Feb) 1944
 - 11 Collip J B Corticotrophic (adrenotropic) thyrotrophic and parathyrotrophic factors *JAMA* 115 2073 2079 (Dec) 1940
 - 12 Deane H W and Greep R O A cytochemical study of the adrenal cortex in hypo and hyperthyroidism *Endocrinology* 41 243 257 (Sept) 1947
 - 13 De Coulon W Ueber Thyreoiden und Hypophysen der Cretinen sowie über Thyreoidreste bei Struma nodosa *Virchows Arch f path Anat* 147 53 99 (Jan) 1897
 - 14 de Quervain F and Wegelin K Der endemische Kretinismus Berlin Springer 1936 pp 101 103

- 15 Emerson K Jr and Cutting W C Urinary thyrotropic hormone *Endocrinology* 23 439 445 (Oct) 1938
- 16 Evans H M and Simpson M E Different effects secured from intraperitoneal as contrasted with subcutaneous administration of the anterior hypophyseal hormones *Anat Rec* 45 215 (Apr) 1930
- 17 Fleischmann W and Shumacker H II The relationship between serum cholesterol and total body cholesterol in experimental hyper and hypothyroidism *Bull Johns Hopkins Hosp* 71 175 183 (Sept) 1942
- 18 Folley S J and Malpress F H Hormonal Control of Lactation *The Hormones* ed by G Pincus and K V Thimann New York Acad Press 1943 pp 767 773
- 19 Frederiksen H and Rydin H The thyroid ovarian correlation in the rabbit *Acta physiol Scandinav* 14 136 143 (Jan Feb) 1947
- 20 Gilligan D R and Abrams M Carbohydrate metabolism in human hypothyroidism induced by total ablation of the thyroid gland *Am J M Sc* 188 796 801 (Dec) 1934
- 21 Gilligan D R Abrams M I and Stern B Carbohydrate metabolism in human hypothyroidism induced by total thyroidectomy part I *Am J M Sc* 188 790 796 (Dec) 1934
- 22 Gley E Sur la suppléance suppoée de la glande thyroïde par le thymus *Compt rend Soc de biol* 49 528 529 (June) 1894
- 23 Gley E and Quinquaud A Contribution à l'étude des interrelations humérales I Action de l'extrait thyroïdien et en général des extraits d'organes sur la sécrétion surrénale *Arch Internat de physiol* 14 152 174 1914
- 24 Greubach W E and Purves H D Studies on experimental goitre pituitary function in relation to goitrogenesis and thyroidectomy *Brit J Exper Path* 24 174 184 (Oct) 1943
- 25 Gudernatsch J F Fütterungsversuche an Amphibienlarven *Zentralbl f Physiol* 26 323 325 1912
- 26 Guyer M F and Claus P E Vacuolation of anterior pituitary gland following castration implantation of cancer tissue and thyroidectomy *Anat Rec* 67 145 155 (Jan) 1937
- 27 Hammett F S Studies of thyroid apparatus effect of thyro parathyroidectomy on reproduction in albino rat *J Metabolic Research* 2 417 427 (Oct) 1927
- 28 — Thyroid and growth *Quart Rev Biol* 4 353 372 (Sept) 1929
- 29 Herring P T The effects of thyroidectomy upon the mammalian pituitary *Quart J Exper Physiol* 1 281 285 1908
- 30 — The effects of thyroidectomy and thyroid feeding upon the adrenalin content of the suprarenals *Quart J Exper Physiol* 9 391 401 1915 1916
- 31 — Influence of thyroids on functions of suprarenals *Endocrinology* 4 577 (Oct Dec) 1920
- 32 Hertz S and Oastler E E Assay of blood and urine for thyrotropic hormone in thyrotoxicosis and myxedema *Endocrinology* 20 520 525 (July) 1936
- 33 Hofmeister F Experimentelle Untersuchungen über die Folgen des Schilddrüsenverlustes *Beitr z klin Chir* 11 441 523 1894
- 34 Hohlweg W and Junkmann K Über die Beziehungen zwischen Hypophysenvorderlappen und Schilddrüse *Arch f d ges Physiol* 232 148 153 1933
- 35 Hoskins E R and Hoskins M M Growth and development of amphibia as affected by thyroidectomy *J Exper Zool* 79 1 69 (Aug) 1919
- 36 — Inter relation of thyroid and hypophysis in growth and development of frog larvae *Endocrinology* 4 1 32 (Jan Mar) 1910
- 37 Hoskins E R and Morris M On thyroidectomy in amphibia *Anat Rec* 11 363 (Jan) 1916 1917
- 38 Jeandelize P Lucien M and Pensol J Modifications du poids du thymus après la thyroïdectomie chez le lapin *Compt rend Soc de biol* 66 942 1909
- 39 Kunde M M Carlson A J and Proud T Ovary in experimental hypo and hyperthyroidism influence of experimental hyperthyroidism on gestation *Am J Physiol* 88 74 753 (May) 1929
- 40 Lee M O Studies on oestrous cycle in rat effect of thyroidectomy *Endocrinology* 9 410 420 (Sept Oct) 1925
- 41 — Studies on oestrous cycle in rat effect of thyroparathyroidectomy and parathyroidectomy *Endocrinology* 10 43 55 (Jan Feb) 1926
- 42 Leonhardt M Experimentelle Untersuchungen über die Bedeutung der Schilddrüse für das Wachstum in Organismus Virchow's *Arch f path Anat* 149 341 377 1897
- 43 Loeser A Die schilddrüsenwirksame Substanz des Hypophysenvorderlappens *Arch f exper Path u Pharmacol* 176 697 728 1934
- 44 MacCallum W G and Fabjan M On the anatomy of a myxoedematous idiot *Bull Johns Hopkins Hosp* 18 341 345 (Sept) 1907
- 45 Mahoney W and Sheehan D Effect of total thyroidectomy upon experimental diabetes insipidus in dogs *Am J Physiol* 112 250-255 (June) 1935
- 46 Marine D Physiology and principal interrelations of thyroid *JAMA* 104 2250-2 55 (June) 1935
- 47 — Physiology and principal interrelations of thyroid gland *Bull New York Acad Med* 15 790 804 (Dec) 1939
- 48 Marine D Manley O T and Baumann E J Influence of thyroidectomy gonadectomy suprarenalectomy and splenectomy on thymus gland of rabbits *J Exper Med* 40 429-443 (Oct) 1924
- 49 Marine D and Rosen S H Effects of cryptorchidism and castration on exophthalmos in rabbits and guinea pigs *Am J Physiol* 121 620 624 (Mar) 1938
- 50 Marine D Rosen S H and Spark C Effect of iodine and de iodinated thyroid on anterior pituitary of goitrous and thyroidectomized rabbits *Proc Soc Exper Biol & Med* 32 803 810 (Feb) 1935
- 51 Mott F W The changes in the central nervous system in hypothyroidism *Proc Roy Soc Med (Sec Path)* 10 51 59 (Feb) 1917
- 52 Nüppe B *Traité du goitre et du crétinisme* Paris Baillière pp 30 48
- 53 Packard F A and Hand A A contribution to the pathological anatomy of sporadic cretinism *Am J M Sc* 122 289 297 (Sept) 1901
- 54 Rawson R W and Starr P Direct measurement of height of thyroid epithelium method

- of a say of thyrotropic substance: clinical application Arch Int Med 61 726 738 (May) 1938
- 55 Reese J D., Koneff A. A., and Wainman P. Cytological differences between castration and thyroidectomy basophils in rat hypophysis Essays in Biology pp 471-485 1943
 - 56 Reuss R. S. Rings H. E. Thorn G. W. and Forsham P. H. The Adrenal Thyroid Relationship Proc of the First Clinical ACTH Conference Philadelphia Blakiston 1950 pp 193 210
 - 57 Richter C. P. Role played by thyroid gland in production of gross body activity Endocrinology 17 73 87 (Jan Feb) 1933
 - 58 Rogers J. H. The effect of the extirpation of the thyroid upon the thymus and the pituitary glands of *Rana pipiens* J Exper Zool 24 589 603 1917 1918
 - 59 Ros H. Die Beziehungen d. r. Schilddrüse zur Fortpflanzung Arch f. Entwicklungsmech d. Organ 137 773 803 1938
 - 60 Rogowitsch N. Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse Anat. u. z. allg. Path 4 453-460 1883 1889
 - 61 Salmon T. N. Effect of thyro parathyroidectomy in new born rats Proc Soc Exper Biol & Med 35 489-491 (Dec) 1936
 - 62 Schönmann A. Hypophysis und thyroidea Virchow's Arch f. path. Anat 129 310-336 (Aug) 1892
 - 63 Schultze W. H. Todliche Menorrhagie in einem Falle von Thyreoplasie mit Hauptzellenadenom der Hypophyse Virchow's Arch f. path. Anat 216 443-452 (June) 1914
 - 64 Schwarz C. Über die Beziehungen der Schilddrüse zum Blutzuckergehalt und zur Glykogen-speicherung Biochem. Ztschr 293 295 301 (Oct) 1937
 - 65 Severinghaus A. E. Cytological study of anterior pituitary of rat with special reference to Golgi apparatus and to cell relationship Anat Rec 57 149 175 (Sept) 1933
 - 66 — Cytology of pituitary gland Proc A. Research Nerv. & Ment. Dis 17 69 117 1936
 - 67 — Cellular changes in anterior hypophysis with special reference to its secretory activities Physiol Rev 17 556 588 (Oct) 1937
 - 68 — The cytology of the pituitary gland Pituitary Gland pp 69 117 Baltimore Williams & Wilkins 1938
 - 69 — Some interrelationships of pituitary gland and thyroid West J Surg 50 371 381 (Aug) 1942
 - 70 Severinghaus A. E. Smelser G. K. and Clark H. M. Anterior pituitary changes in adult male rats following thyroxine injections or thyroid feeding Proc Soc Exper Biol & Med 31 1127 1129 (June) 1934
 - 71 Smelser G. K. Effect of thyroidectomy on testicular function Anat Rec 60 (Suppl. 13) 53 1934
 - 72 — Effect of thyroidectomy on reproductive system and hypophysis of adult male rat Anat Rec 74 7 16 (May) 1939
 - 73 Smith P. E. and Engle E. T. The influence of thyroidectomy upon the amount of gonadal stimulating hormone present in the anterior hypophysis Anat Rec 45 278 279 (Apr) 1930
 - 74 Spence A. W. Oestrin in toxic goiter Lancet 910 974 (Oct) 1936
 - 75 Stein K. F. and Lisle M. Gonad stimulating potency of pituitary of hypothyroid young male rats Endocrinology 30 16-24 (Jan) 1942
 - 76 Stueda H. Ueber das Verhalten der Hypophyse des Kaninchens nach Entfernung der Schilddrüse Beitr. z. path. Anat. u. z. allg. Path 7 537 552 1890
 - 77 Swann H. G. and Johnson P. E. Thyroid function in diabetes insipidus in rat Endocrinology 24 397-403 (Mar) 1939
 - 78 Thompson W. O., Taylor S. G., III Thompson P. K., Nadler S. M. and Dickie L. F. Calorigenic action of extracts of anterior lobe of pituitary in man Endocrinology 20 5 63 (Jan) 1936
 - 79 Trautmann A. Hypophyse und Thyroidea, tome Frankl. Ztschr. f. Path 18 173 304 1916
 - 80 Uhlenhuth E. Relation between thyroid gland metamorphosis and growth J. Gen. Physiol 1 473-487 (Mar) 1919
 - 81 Van Dyke H. B. and Chen E. Production of ovulation by anterior lobe of pituitary of thyroidectomized rabbit Proc Soc Exper Biol & Med 31 377 378 (Dec) 1933
 - 82 Van Horn W. M. Relation of thyroid to hypophysis and ovary Endocrinology 17 152 162 (Mar Apr) 1933
 - 83 Wegelin C. Zur Kenntnis der Kachexia thyreopriva Virchow's Arch f. path. Anat 254 689 699 1913
 - 84 Wilkins L. Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 10th Meeting June 15 16 New York Josiah Macy Jr. Foundation 1943 pp 98 124
 - 85 Zeckwer I. T., Davidson L. W., Keller T. B. and Livingood C. S. Jr. Pituitary in experimental cretinism: structural changes in pituitaries of thyroidectomized rats Am J. M. Sc 190 145 157 (Aug) 1935

II Hyperhormonal Effects

- 1 Aron M. L'hormone thyroïdienne stimulant de la préhypophyse est-elle éliminée par le rein et présente dans l'urine? Compt. rend. Soc. de biol 114 20-23 1933
- 2 Blackford J. M. Thyroid intoxication North West Med. 18 199 201 (Oct) 1919
- 3 Capelle E. Ein neuer Beitrag zur Basedowthyreose München med. Wchnschr 55 1826 1828 1908
- 4 Cohen R. H. Effect of experimentally produced hyperthyroidism upon reproductive and associated organs of male rat, Am J. Anat 56 143 159 (Jan) 1935
- 5 Deane H. W. and Greep R. O. A cytochemical study of the adrenal cortex in hypo and hyperthyroidism Endocrinology 41 243 257 (Sept) 1947
- 6 Hashimoto H. Influence of thyroid feeding upon physiological action of pancreas Endocrinology 4 56 (Jan-Mar) 1920
- 7 Herrng P. T. The adrenal content of the suprarenals of the female white rat and the changes brought about by thyroid feeding and other conditions Quart J. Exper. Physiol 11 115 123 1920
- 8 — Influence of thyroids on functions of suprarenals Endocrinology 4 577 (Oct-Dec) 1910
- 9 Hildebrand O. Erfahrungen und Studien über die Basedow'sche Krankheit und ihre operative

- Behandlung Arch f klin Chir 111 170 (Nov.) 1918
- 10 Hoskins H G Thyroid secretion as a factor in adrenal activity JAMA 55 1724 1725 (Nov.) 1910
 - 11 — The interrelation of the organs of internal secretion Am J M Sc 141 374 385 (Mar.) 1911
 - 12 Ingle D J and Higgins G M Effect of thyroxine on extent of regeneration in enucleated adrenal gland of rat Endocrinology 23 419 423 (Oct.) 1938
 - 13 Kojima M On morphogenetic changes in the pancreas produced by thyroid and pituitary feeding J Physiol 50 14 (July) 1916
 - 14 Marine D Physiology and principal interrelations of thyroid gland Bull New York Acad Med 15 790 804 (Dec.) 1939
 - 15 Marine D Rosen H and Spark C Effect of iodine and desiccated thyroid on anterior pituitary of goitrous and thyroidectomized rabbits Proc Soc Exper Biol & Med 32 803 810 (Feb.) 1935
 - 16 Preston M I Effects of thyroxin injections on suprarenal glands of mouse Endocrinology 12 323 334 (May June) 1938
 - 17 Reforzo Membrives J Thyroid inhibiting action of hypophyses of rats fed with thyroid Endocrinology 32 263 270 (Mar.) 1943
 - 18 Severinghaus A F Some interrelationships of pituitary gland and thyroid West J Surg 50 371 381 (Aug.) 1942
 - 19 Severinghaus A E Smelser G K and Clark H M Anterior pituitary changes in adult male rats following thyroxin injections or thyroid feeding Proc Soc Exper Biol & Med 31 1127 1129 (June) 1934
 - 20 Smelser G K Testicular function in hyperthyroidism Anat Rec 70 (Suppl 63) 1937
 - 21 Speidel C C Studies of hyperthyroidism: significance of changes in thymus glands of thyroid treated frog tadpoles Am J Anat 37 141 157 (Mar.) 1936
 - 22 Squier T L and Grabfield G P Adrenal enlargement in rabbits Endocrinology 83 101 (Jan Feb) 1922
 - 23 Swann H G and Johnson P E Thyroid function in diabetes insipidus in rat Endocrinology 24 397 403 (Mar.) 1939
 - 24 Tobin C Some effects of thyrotropic hormone on reproductive system of normal thyroidectomized or adrenalectomized female rats Endocrinology 30 227 233 (Feb.) 1947
 - 25 Tyndale H H and Levin L Ovarian weight responses to menopause urine injections in normal hypophysectomized and hypophysectomized thyroxin treated immature rats Am J Physiol 120 486 493 (Nov.) 1937
 - 26 Uotila U U Regulation of thyrotropic function by thyroxin after pituitary stalk section Endocrinology 26 129 135 (Jan.) 1940
 - 27 Van Horn W M Relation of thyroid to hypophysis and ovary Endocrinology 17 152 167 (Mar Apr) 1933
- E Histophysiology**
- 1 Chaikoff I L and Taurog A Studies on the formation of organically bound iodine compounds in the thyroid gland and their appearance in plasma as shown by the use of radio active iodine Ann New York Acad. Sc. 50 377 402 (Jan.) 1949
 - 2 Dempsey E W Fluorescent and histochemical reactions in rat thyroid gland at different states of physiological activity Endocrinology 11 27 38 (Jan.) 1944
 - 3 de Robertis F Proteolytic enzyme activity of colloid extracted from single follicles of rat thyroid Anat Rec 80 219 231 (June) 1941
 - 4 — Intracellular colloid in initial stages of thyroid activation Anat Rec 84 125 131 (Oct.) 1942
 - 5 — Proteolytic activity in the physiologic pathology and therapeutics of the thyroid gland West J Surg 56 253 269 (May) 1949
 - 6 — Cytological and cytochemical bases of thyroid function Ann New York Acad Sc. 50 317 335 (Jan.) 1949
 - 7 de Robertis F and Goncalves J M Oxidation reduction potential of thyroid follicle in normal and experimental conditions Endocrinology 36 245 250 (Apr.) 1945
 - 8 de Robertis F and Grasso R Peroxidase activity of thyroid gland under normal and experimental conditions Endocrinology 38 146 147 (Mar.) 1946
 - 9 de Robertis E and Nowinski W W Proteolytic activity of normal and pathological human thyroid tissue J Clin Endocrinol 6 235 246 (Mar.) 1946
 - 10 — Mechanism of therapeutic effect of iodine on thyroid gland Science 103 421-472 (Apr.) 1946
 - 11 Dziemian A J Proteolytic activity of thyroid gland J Cell & Comp Physiol 21 339 345 (June) 1943
 - 12 Franklin A L Chaikoff I L and Lerner S R Influence of goitrogenic substances on conversion *in vitro* of inorganic iodide to thyroxine and diiodotyrosine by thyroid tissue with radioactive iodine as indicator J Biol Chem 153 151 162 (Apr.) 1944
 - 13 Gersh I and Caspersen T Total protein and organic iodine in colloid and cells of single follicles of thyroid gland Anat Rec 78 303 319 (Nov.) 1940
 - 14 Harrington C R and Pitt Rivers R V Chemical conversion of diiodotyrosine into thyroxine Biochem J 39 157 164 (Feb.) 1945
 - 15 Leblond C P Histological localization of radioactive compounds in tissue as illustrated with the help of radioiodine Recent Progress in Hormone Research Vol 3 pp 159 169 New York Acad Press 1948
 - 16 Lerman J and Salter W T The behavior of natural and artificial thyroid protein with an attempt at biochemical interpretation of the effect of iodine in thyroid disease Tr Am Assn for Study of Goiter pp 143 152 1916
 - 17 Reineke E P and Turner C W Effect of certain experimental conditions on formation of thyroxine from diiodotyrosine J Biol Chem 162 369 375 (Feb.) 1946
 - 18 Salter W T Endocrine Function of Iodine p 11 Cambridge Harvard 1940
 - 19 Salter W T and Lerman J The genesis of thyroid protein: clinical assays of artificial thyroid protein in human myxedema Endocrinology 20 801 808 (Nov.) 1936
 - 20 Wahlberg J Histophysiology of the thyroid West J Surg Obst & Gynec 55 19 (Jan) 1947

- 21 Williams R G Microscopic studies of living thyroid follicles implanted in transparent chambers installed in rabbits ear *Am J Anat* 62 1 29 (Nov) 1937

F Activity at Different Periods in Life

- 1 Abelin I Über die extrathyreoidale Entstehung thyronartiger wirkender Jodverbindungen *Abh Wehnscr* 13 940 942 (June) 1934
- 2 Andrews L N and Schnetler L M Effect of feeding thyroacetic to hens upon the thyroid gland of chicks *Endocrinology* 37 38 384 (Nov) 1945
- 3 Carruthers D G Congenital deaf mutism as a sequela of a rubella like maternal infection during pregnancy *M J Australia* 1 315 320 (Mar) 1945
- 4 Carter G S Iodine compounds and fertilisation *J Exper Biol* 9 253 260 (July) 1932
- 5 Chapman A F Extrathyroidal iodine metabolism *Endocrinology* 29 686 694 (Nov) 1941
- 6 Chapman H M Corner G W Robinson D and Evans H D The collection of radio active iodine by the human fetal thyroid *J Clin Endocrinol* 8 717 720 (Sept) 1948
- 7 Chapman A Higgins G M and Mann F C Additional studies of extrathyroidal metabolism of iodine *J Endocrinol* 3 392 396 (May) 1944
- 8 de Quervain F and Wegehen C *Der endemische Kretinismus* p 206 Berlin Springer 1936
- 9 Doderlein G Weitere experimentelle Untersuchungen über die Wirkung des thyreotropen Hormons des Hypophysenvorderlappens *Arch f Gynak* 185 22 35 1933
- 10 Dorff G B Sporadic cretinism in one of twins report of cases with roentgen demonstration of osseous changes that occurred in utero *Am J Dis Child* 48 1316 1325 (Dec) 1934
- 11 Gorbman A and Evans H M Bermaning of function in thyroid of fetal rat *Endocrinology* 32 113 115 (Jan) 1943
- 12 Gregg N M Congenital cataract following German measles in mother *Tr Ophth Soc Australia (Brit M A)* 3 35 1941
- 13 — Rubella during pregnancy of mother with its sequelae of congenital defects in child *M J Australia* 1 313 315 (Mar) 1945
- 14 Hart E B and Steenbock H Hairless pig malady *J Biol Chem* 33 313 (Feb) 1918
- 15 Hosen H Thyroid deficiency in twins *J Pediat* 16 210 214 (Feb) 1940
- 16 Hughes A M Cretinism in rats induced by thyroacetic *Endocrinology* 34 69 71 (Jan) 1944
- 17 Hurthall L M and Musulin N Cretinism *Am J Med* 1 56 82 (July) 1946
- 18 Ingalls T H and Davies J A Mongolism following intercurrent infectious disease in pregnancy *New England J Med* 236 437 438 (Mar) 1947
- 19 Man E B Culotta C S Siegfried D A and Stilson C Serum precipitable iodines in recognition of cretinism and as control of thyroid medication *J Pediat* 31 154 160 (Aug) 1947
- 20 Marine D and Lenhart C H Effects of the administration or the withholding of iodine containing compounds in normal colloid or actively hyperplastic (parenchymatous) thyroids of dogs some experiments on (congenital) prenatal thyroid hyperplasia in dogs remarks on the clinical manifestations associated with marked thyroid hyperplasia *Arch Int Med* 4 253 270 (Sept) 1909
- 21 McClelland J F and McLennan C E Hormone iodine in mother's and umbilical cord blood *Proc Soc Exper Biol & Med* 40 553 (Apr) 1939
- 22 Morton M E Chaskoff I L and Rosenfeld S Inhibiting effect of inorganic iodide on formation in vitro of thyroxine and diiodotyrosine by surviving thyroid tissue *J Biol Chem* 154 381 387 (July) 1944
- 23 Neumann H O Klinische und pathologische anatomische Studien zum Problem der Neugeborenen Schilddrüse *Arch f Gynak* 163 368 405 1937
- 24 Parkin G and Greene J A Pregnancy occurring in cretinism and in juvenile and adult myxedema *J Clin Endocrinol* 3 466 468 (Aug) 1943
- 25 Patterson W H Hunt H F and Nicodemus R F Evidence that most thyroid disease is congenital *West J Surg* 45 486 499 (Sept) 1937
- 26 Perkin H J and Brown H R Influence of thyroid gland and of ovary on metabolism of iodine experimental study in dog *Endocrinology* 22 538 542 (May) 1938
- 27 Rumph P and Smith P L First occurrence of secretory products and of a specific structural differentiation in the thyroid and anterior pituitary during the development of the pig foetus *Anat Rec* 33 289 298 (Apr) 1926
- 28 Sachs M G On the causes of sterility in experimental athyreosis *Bull Biol et med exper URSS* 7 521 523 1939
- 29 Salter W T *Endocrine Function of Iodine* p 13 Cambridge Harvard Monographs 1940
- 30 *Ibid* p 150
- 31 *Ibid* p 155
- 32 Schittenhelm A and Esler H Zur Frage der Übertragung des thyreotropen Hormons durch die Placenta und die Milch *Ztschr f d ges exper Med* 21 124 125 1935
- 33 Schlotthauer C F and Caylor H D Effect of thyrorectomy and of certain diets on pregnant swine and their off spring *Am J Physiol* 89 608 609 (Aug) 1929
- 34 Sharpless G R New goster producing diet for rat *Proc Soc Exper Biol & Med* 38 166 168 (Feb) 1938
- 35 Silberberg M and Silberberg R Effect of potassium iodide on bone and cartilage in thyrorectomized immature guinea pigs *Arch Path* 28 846 850 (Dec) 1939
- 36 Swan C Tostevin A L Mayo H and Black G H B Congenital defects in infants following infectious diseases during pregnancy with special reference to relationship between German measles and cataract deaf mutism heart disease and microcephaly and to period of pregnancy in which occurrence of rubella is followed by congenital abnormalities *M J Australia* 2 201 210 (Sept) 1943
- 37 — Further observations on congenital defects in infants following infectious diseases during pregnancy with special reference to rubella *M J Australia* 1 409 413 (May) 1944
- 38 Thérèse S De la perméabilité du placenta aux

- hormones thyroïde et thyroïdope Bull biol et méd exp URSS 7 544 548 1939
- 34 Trendelenburg P Die Hormone p 213 Berlin Springer 1934
 - 40 Wagner Jauregg J Ist das Entstehen des Kretinismus durch intrauterine Behandlung der Frucht zu verhüten? Schweiz med Wchn chr 68 246 247 (Mar) 1938
 - 41 Whiteside B Effect of thyrotropic hormone upon pregnant rabbits Endocrinology 26 136 141 (Jan) 1940
 - 42 Williams R H Further studies of absorption distribution and elimination of thiouracil J Clin Endocrinol 4 385 393 (Aug) 1944
 - 43 Zondek H On problem of foetal function of thyroid gland, Acta med Scandinav 103 251 258 1940
- ### G Antithyroid Drugs
- 1 Baumann E J and Marine D Involution of the adrenal cortex in rats fed with thiouracil Endocrinology 36 400-405 (June) 1945
 - 2 Freiesleben L and Kjerulf Jensen K Effect of 6 methyl 2 thiouracil on rat foetuses and infantile rats Acta pharmacol et toxicol 2 307 316 (Apr) 1946
 - 3 Goldsmith E D Gordon A S and Chappier H A An analysis of the effects of continued thiourea treatment in pregnancy and on the development of the offspring in the rat Am J Obst & Gynec 49 197 206 (Feb) 1945
 - 4 May L G, Moseley R W and Forbes J C Effect of thiourea on body fat and liver glycogen of rats Endocrinology 38 147 151 (Mar) 1946
 - 5 Paschke K E Cantarow A Rakoff A E and Tilson E K Thiouracil levels in serum and urine J Pharmacol & Exper Therap 83 270 274 (Apr) 1945
 - 6 Riker W F and Wescoe W C The pharmacology and therapeutic applications of anti thyroid compounds Am J M Sc 210 665 679 (Nov) 1945
 - 7 Williams R H Further studies of the absorption distribution and elimination of thiouracil J Clin Endocrinol 4 385 393 (Aug) 1944
 - 8 Williams R H and Bissell G W Thiouracil in the treatment of thyrotoxicosis New England J Med 229 97 108 (July) 1943
 - 9 Williams R H Kay G A and Jandorf B J Thiouracil its absorption distribution and excretion J Clin Investigation 23 613 627 (Sept) 1944
 - 10 Williams R H and Kay G A Absorption distribution and excretion of thiourea Am J Physiol 143 715 722 (May) 1945
 - 11 — Thiouracils and thioureas Arch Int Med 80 37 52 (July) 1947
 - 12 Williams R H Weinglass A R and Kay G A Thiouracil storage in thyroid as affected by thyrotropic hormone and potassium iodide Am J M Sc 207 701 705 (June) 1944
- ### VII CHEMISTRY
- 1 Carter G S Iodine compounds and fertilization J Exper Biol 9 253 270 (July) 1932
 - 2 Harrington C R Chemistry of thyroxine Biochem J 20 293 313 1926
 - 3 Heidelberg M and Svedberg T Molecular weight of thyroglobulin Science 80 414 (Nov) 1934
 - 4 Heidelberg M and Pedersen K O Molecular weight and isoelectric point of thyroglobulin J Gen Physiol 19 95 108 (Sept) 1935
 - 5 Jailer J W, Sperry W M Engle E T and Smeler G K Experimental hypothyroidism in monkey Endocrinology 35 27 37 (July) 1944
 - 6 Lerman J Iodine components of blood circulating thyroglobulin in normal persons and in persons with thyroid disease J Clin Investigation 19 555 560 (July) 1940
 - 7 Lerman J and Salter W T Relief of myxedema with proteins of extrathyroidal origin Endocrinology 25 712 720 (Nov) 1939
 - 8 McClendon J F and Foster W C Thyroid hormone in blood and tissues in relation to basal metabolic rate Endocrinology 28 411 418 (Mar) 1941
 - 9 Means J H The Thyroid and Its Diseases, p 61 Philadelphia Lippincott 1937
 - 10 Ibid p 63
 - 11 Morton M E Chaikoff I L Reinhardt, W O and Anderson E Radioactive iodine as indicator of metabolism of iodine formation of thyroxine and diiodotyrosine by completely thyroidectomized animal J Biol Chem 147 751 769 (Jan) 1943
 - 12 Perkin H J and Brown B R Influence of thyroid gland and of ovary on metabolism of iodine experimental study in dog Endocrinology 22 538 547 (May) 1938
 - 13 Salter W T The metabolic circuit of the thyroid hormone Ann New York Acad Med 50 358 373 (Jan) 1949
 - 14 Salter W T, and Lerman J Genesis of thyroid protein clinical assays of artificial thyroid protein in human myxedema Endocrinology 20 801 808 (Nov) 1936
 - 15 Salter W T and Pearson O H Enzymic synthesis from thyroid diiodotyrosine peptide of artificial protein which relieves myxedema J Biol Chem 112 579 589 (Jan) 1936
 - 16 Schneider E and Widmann E Klinische und experimentelle Untersuchungen zum Problem des Kropfes und der Basedowschen Krankheit, Deutsche Zeitschr f Chir 238 206 215 1932
 - 17 Taugo A and Chaikoff I L Nature of circulating thyroid hormone J Biol Chem 176 639 656 (Nov) 1943
 - 18 Zondek H The Disease of the Endocrine Glands ed 4 pp 32 33 Baltimore Williams & Wilkins 1944
- ### VIII BIO ASSAY
- 1 Cameron A T and Carmichael J Biochemistry of iodine effect of thyroxine on growth in white rats and in rabbits J Biol Chem 46 35 53 (Mar) 1921
 - 2 — Contributions to biochemistry of iodine comparative effects of thyroid and iodide feeding on growth in white rats and in rabbits J Biol Chem 45 69 (Dec) 1920
 - 3 Gaddum J H Quantitative observations on thyroxine and allied substances effects on oxygen consumption of rats J Physiol 68 383 405 (Jan) 1930
 - 4 Gudernatsch J F Feeding experiments on tadpoles II A further contribution to the knowledge of organs with internal secretion, Am J Anat 15 451 480 (Jan) 1914
 - 5 Harrington, C R and Randall S S Chemical

- assay of thyroid gland Quart J Pharm & Pharmacol 2 501 506 (Oct-Dec) 1929
- 6 Hunt R Acetonitrile test for thyroid and of some alterations of metabolism Am J Physiol 63 25, 299 (Jan) 1923
 - 7 — Standardization of thyroid preparations Arch Int Med 35 671 686 (June) 1923
 - 8 — The influence of thyroid feeding upon poisoning by acetonitrile J Biol Chem 1 33 44 1905 1906
 - 9 Means J H The Thyroid and Its Diseases pp 31 61 Philadelphia Lippincott 1948
 - 10 Shackell L F Assay of thyroid USP by determination of oxygen consumption in guinea pig J Pharmacol & Exper Therap 60 117 118 (Apr) 1937
 - 11 Swingle W W Studies on the relation of iodine to the thyroid J Exp Zool 27 397-425 (Jan) 1919
- ### IX PATHOLOGY
- 1 Albert A Rawson R W Merrill P Lennon B and Riddell C Reversible inactivation of thyrotropic hormone by elemental iodine I The action of iodine J Biol Chem 166 637 647 (Dec) 1946
 - 2 Albert A Rawson R W Riddell C Merrill P, and Lennon B In vivo augmentation of thyrotropic hormone and partial reactivation of iodinated (inactive) thyrotropic hormone extract by goitrogens Endocrinology 40 361 369 (June) 1947
 - 3 Arnott D G Emery E W Fraser R and Hob on Q J G Urinary excretion of radio active iodine as a diagnostic test in thyroid disease Lancet 2 456-465 (Sept) 1949
 - 4 Astwood E B Mechanisms of action of various antithyroid compounds Ann New York Acad Sci 50 419-443 (Jan) 1949
 - 5 Astwood E B Sullivan J Busell A and Tyslowitz R Action of certain sulfonamides and of thiourea upon function of thyroid gland of rat Endocrinology 32 210 225 (Feb) 1943
 - 6 Astwood E B and Stanley M M Radio active iodine and thyroid function West J Surg 55 615 639 (Dec) 1947
 - 7 Bachromejew J R and Ter Ossipowa N A Zur Frage der sekretorischen Innervation des Schilddrüsensapparates (Eine physiologisch histologische Untersuchung) Endokrinologie 15 404 415 1935
 - 8 Baumann E J Metzger N and Marne D Mode of action of thiourea on thyroid gland of rabbits Endocrinology 34 44 49 (Jan) 1944
 - 9 Chagas C de Robertis E and Courcero A Penetration of radioactive iodine in thyroid gland colloid Texas Rep Biol & Med 3 170 178 1945
 - 10 Chapman A Relation of thyroid and pituitary glands to iodine metabolism Endocrinology 29 680 685 (Nov) 1941
 - 11 Cope O Rawson R W and McArthur J W The hyperfunctioning simple adenoma of the thyroid Surg Gynec & Obst 84 415 426 (Apr) 1947
 - 12 Dempsey E W Fluorescent and histochemical reactions in rat thyroid gland at different states of physiological activity Endocrinology 34 27 38 (Jan) 1944
 - 13 de Robertis E The intracellular colloid of the normal and activated thyroid gland of the rat studied by the freezing-drying method Am J Anat 68 317 339 (May) 1941
 - 14 — Intracellular colloid in initial stages of thyroid activation Anat Rec 84 125 135 (Oct) 1942
 - 15 — Cytological and cytochemical bases of thyroid function Ann New York Acad Sci 50 317 335 (Jan) 1949
 - 16 de Robertis E and Goncalves J M Oxidation reduction potential of thyroid follicle in normal and experimental conditions Endocrinology 36 245 250 (Apr) 1945
 - 17 de Robertis E and Nowinski W W Mechanism of therapeutic effect of iodine on thyroid gland Science 103 421-422 (Apr) 1946
 - 18 — Proteolytic activity of normal and pathological human thyroid tissue J Clin Endocrinol 8 235 246 (Mar) 1946
 - 19 Drueman A J Proteolytic activity of thyroid gland J Cell & Comp Physiol 21 339 345 (June) 1943
 - 20 Dvoskin Samuel Spontaneous formation of intracellular colloid droplets in surviving chick thyroid tissue Endocrinology 41 403-416 (Nov) 1947
 - 21 Fitzgerald P J, and Foote F W Jr The function of various types of thyroid carcinoma as revealed by the radioautographic demonstration of radioactive iodine (131I) J Clin Endocrinol 9 1153 11 9 (Nov) 1949
 - 22 Franklin A L and Chaikoff I L Effect of sulfonamides on conversion in vitro of inorganic iodide to thyroxine and diiodotyrosine by thyroid tissue with radioactive iodine as indicator J Biol Chem 152 295 301 (Feb) 1944
 - 23 Frantz V A Ball R P Keston A S and Palmer W W Thyroid carcinoma with metastases studied with radioactive iodine Ann Surg 119 663 669 (May) 1944
 - 24 Friedgood H B Similarity of iodine remission in experimental anterior hypophyseal hyperthyroidism hyperthyroidism of acromegaly and that of exophthalmic goiter Endocrinology 20 526 536 (July) 1935
 - 25 Graess R Action of thiourea on intracellular colloid of thyroid gland Anat Rec 95 365 377 (Aug) 1946
 - 26 Griesbach W E Studies on experimental goitre changes in anterior pituitary of rat produced by Brassica seed diet Brit J Exper Path 22 245 249 (Oct) 1941
 - 27 Griesbach W E Kennedy T H and Purves H D Studies on experimental goitre effect of goitrogenic diet on hypophysectomized rats Brit J Exper Path 22 249 254 (Oct) 1941
 - 28 Haines S F Keating F R Jr Power M H Williams M M E and Kelley M P The use of radioiodine in the treatment of exophthalmic goiter J Clin Endocrinol 8 813 825 (Oct) 1948
 - 29 Hamilton J G Rates of absorption of radioactive sodium potassium chloride bromine and iodine in normal human subjects Am J Physiol 124 667 678 (Dec) 1938
 - 30 Hamilton J G and Soley M H Studies in iodine metabolism by use of new radioactive isotope of iodine Am J Physiol 127 557 572 (Oct) 1939
 - 31 — Studies in iodine metabolism of the thyroid gland in situ by the use of radio iodine

- in normal subjects and in patients with various types of goiter *Am J Physiol* 131 135 143 (Nov.) 1940
- 31 Hamilton J G Solev M H Reilly W A and Eichorn K H Radioactive iodine studies in childhood hypothyroidism *Am J Dis Child* 66 495 507 (Nov.) 1943
 - 32 Hart E B and Steenbock H Hairless pig malady *J Biol Chem* 33 313 (Feb.) 1918
 - 33 Hertz S Radioactive iodine as indicator in thyroid physiology observations on rabbits and on goiter patients *Am J Roentgenol* 46 467-468 (Oct.) 1941
 - 34 Hertz S Roberts A and Evans R H Radioactive iodine as indicator in study of thyroid physiology *Proc Soc Exper Biol & Med* 38 510 513 (May) 1938
 - 35 Hertz S Roberts A Means J H and Evans R D Radioactive iodine as indicator in thyroid physiology iodine collection by normal and hyperplastic thyroids in rabbits *Am J Physiol* 128 565 576 (Feb.) 1940
 - 36 Hertz S Roberts A and Salter W T Radioactive iodine as an indicator in thyroid physiology IV The metabolism of iodine in Graves disease *J Clin Investigation* 21 25 29 (Jan.) 1942
 - 37 Hurxthal L M Unpublished data
 - 38 Junquiera L C Action *in vitro* of thyrotropic hormone and iodine on thyroid cells *Endocrinology* 40 286 291 (Apr.) 1947
 - 39 Keating F R Power M H Berkson J and Haines S F The urinary excretion of radioiodine in various thyroid states *J Clin Investigation* 26 1138 1151 (Nov.) 1947
 - 40 Kennedy T H Thio ureas as goitrogenic substances *Nature* 150 233 234 (Aug.) 1942
 - 41 Keston A S Goldsmith F D Gordon A S and Charipper H A Effect of thiourea upon metabolism of iodine by rat thyroid *J Biol Chem* 152 241 244 (Feb.) 1944
 - 42 Klose H Die Chirurgie der basedowschen Krankheit Stuttgart Enke 1929 pp 287 304
 - 43 Leatham J Plasma protein concentrations and organ weights of rats on high protein diet *Endocrinology* 37 157 164 (Sept.) 1945
 - 44 LeBlond C P Behavior of radioiodine in resting and stimulated thyroids *Anat Rec* 88 285 290 (Mar.) 1944
 - 45 LeBlond C P Fertman M H Puppel I D and Curtis G M Radioiodine autoradiography in studies of human goitrous thyroid glands *Arch Path* 41 510 515 (May) 1946
 - 46 LeBlond C P and Gros J Thyroglobulin formation in the thyroid follicle visualized by the coated autograph technique *Endocrinology* 43 306 324 (Nov.) 1948
 - 47 LeBlond C P Puppel I D Riley E Radike M and Curtis G M Radioiodine and iodine fractionation studies of human goitrous thyroids *J Biol Chem* 162 275 285 (Feb.) 1946
 - 48 Loeser A and Thompson K W Hypophyphen vorerlappen Jod und Schilddruse der Mechanismus der Schilddrusenwirkung des Jods *Endokrinologie* 14 144 150 1934
 - 49 Mackenzie C G and Mackenzie J H Effect of sulfonamides and thioureas on thyroid gland and basal metabolism *Endocrinology* 32 185 209 (Feb.) 1943
 - 50 McGinty D A Iodine absorption and utilization under the influence of certain goitrogens *Ann New York Acad Sc* 40 403-418 (Jan.) 1949
 - 51 McGinty D A Rawson R W Fluharty R G Wilson M Riddell C and Yee H Effect of certain goitrogenic drugs on absorption of radioactive iodine by thyroid gland *J Pharm & Exper Therapeutics* 93 246 257 (June) 1948
 - 52 Means J H The Thyroid and its Diseases p 278 Philadelphia Lippincott 1937
 - 53 Morton M E Perlman I Anderson, E and Chaikoff I L Radioactive iodine as indicator of metabolism of iodine effects of hypophysectomy on distribution of labeled thyroxine and diiodotyrosine in thyroid gland and plasma *Endocrinology* 30 493 501 (Mar.) 1942
 - 54 Purves H D and Griesbach W E Studies on experimental goiter VIII Thyroid tumours in rats treated with thiourea *Brit J Exper Path* 28 46 53 (Feb.) 1947
 - 55 Rawson R W Evans R H Mean J H Peacock W C Lerman J and Cortell R E The action of thiouracil upon the thyroid gland in Graves disease *J Clin Endocrinol* 4 111 (Jan.) 1944
 - 56 Rawson R W Hertz S and Means J H Thiocyanate goiter in man *Ann Int Med* 19 829 842 (Dec.) 1943
 - 57 Rawson R W and McArthur J W Radioactive iodine its use as a tool in the study of thyroid physiology *J Clin Endocrinol* 7 230 263 (Apr.) 1947
 - 58 Rawson R W McGinty D A Peacock W Merrill P Wilson M and Lockhart H Effect of certain goitrogenic drugs on absorption of radioactive iodine by thyroid gland of rats and chicks *J Pharm & Exper Therap* 93 240 245 (June) 1948
 - 59 Rawson R W Moore F D Peacock W Means J H Cope O and Riddell C B Effect of iodine on the thyroid gland in Graves disease when given in conjunction with thiouracil A two action theory of iodine *J Clin Investigation* 24 869 877 (Nov.) 1945
 - 60 Rawson R W Tannheimer J F and Peacock W Uptake of radioactive iodine by thyroids of rats made goitrous by potassium thiocyanate and by thiouracil *Endocrinology* 34 245 253 (Apr.) 1944
 - 61 Richter C P and Clusby K H Taste effects of bitter tasting phenylthiocarbamide *Arch Path* 33 46 57 (Jan.) 1942
 - 62 Riker W F and Wescoe W C The pharmacology and therapeutic applications of anti thyroid compounds *Am J Med Sc* 210 663 679 (Nov.) 1945
 - 63 Salter W T *Endocrine Function of Iodine* p 137 Cambridge Harvard Press 1940
 - 64 Seidlin S M Marinelli L D and O'Byrne E Radioactive iodine therapy effect on functioning metastases of adenocarcinoma of the thyroid *JAMA* 132 838 847 (Dec.) 1946
 - 65 Skanse B Radioactive iodine its use in studying the urinary excretion of iodine by humans in various states of thyroid function *Acta med Scandina* 131 251 268 1948
 - 66 Smith G E Fetal and maternal atrophy, *Endocrinology* 3 262 272 (July, Sept.) 1919
 - 67 Stanley M M The use of radioactive iodine in the study of normal and abnormal thyroid function *Bull New England Med Center* 10 28 38 (Feb.) 1948

69 Stephens D J Effect of thyrotropic principle on anterior pituitary on thyroid of undernourished guinea pig *Endocrinology* 26 485 492 (Mar) 1930

70 Taurog A Chalkoff I L and Bennett L L Influence of hypophysectomy upon plasma iodine and thyroxine content of thyroid gland of rat *Endocrinology* 38 122 126 (Feb) 1946

71 Thomas O L Cytological study of secretion antecedents of rat thyroid activated in thiourea *Anat Rec* 89 461-473 (Aug) 1944

72 Wahlberg J Histophysiology of the thyroid *West J Surg* 55 1 10 (Jan) 1947

73 Williams R H Jaffe H and Bernstein B Comparisons of the distribution of radio active iodine in serum and urine in different levels of thyroid function *J Clin Investigation* 28 1222 1227 (Sept) 1949

XIII EXAMINATION OF PATIENT

1 Bartels E C Profound myxedema with normal plasma cholesterol *Lahey Clin Bull* 5 137 142 (July) 1947

2 — Basal metabolism under pentothal anesthesia *J Clin Endocrinol* 9 1190 1201 (Nov) 1949

3 Bartels E C and Helden G O Basal metabolic rate in aortic stenosis *Lahey Clin Bull* 7 8 12 (July) 1950

4 Blumgart H L Gargill S I and Gilligan D R Studies on velocity of blood flow

circulatory response to thyrotoxicosis *J Clin Investigation* 9 69 89 (Aug) 1930

5 de Roberts E Assay of thyrotrophic hormone *J Clin Endocrinol* 4 956 966 (Nov) 1948

6 Du Bois E F *Basal Metabolism in Health and Disease* pp 372 Philadelphia Lea & Febiger 1924

7 Hursthal L M and Simpson H N Hypothyroidism hypercholesterolemia *J Clin Endocrinol* 1 450-452 (May) 1941

8 Hursthal L M and Perkin H J The fractionation of the iodine of the blood in thyroid disease *J Clin Investigation* 18 733 757 (Nov) 1939

9 Kirk E and Kiørning S A Hypometabolism *Acta med Scandinav Suppl* 184 pp 1 83 1946

10 Kumpke C and Stein W R Aortic stenosis analysis of 106 proved cases *J Lab & Clin Med* 32 324 325 (Mar) 1947

11 Lahey F H Quadriceps test for myasthenia of hyperthyroidism *JAMA* 87 754 (Sept) 1926

12 Salter W T *The Endocrine Function of Iodine* p 288 Cambridge Harvard 1940

13 — The metabolic circuit of the thyroid hormone *Ann New York Acad Sc* 50 358 376 (Jan) 1949

14 Smith J A and Levine S A Aortic stenosis with elevated metabolic rate simulating hyperthyroidism *Arch Int Med* 80 265 270 (Aug) 1947



FIG 113 THYROID GLAND This specimen demonstrates the shape of the thyroid and the pyramidal lobe. Actually it is the hyperplastic gland of Graves's disease removed in total at operation.

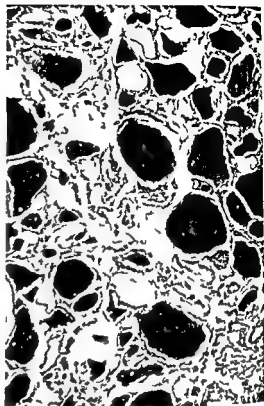


FIG 114 THYROID Normal adult thyroid gland

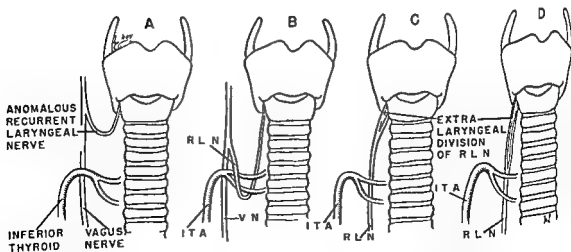


CHART 27 RECURRENT LARYNGEAL NERVE (RIGHT) SHOWING ANOMALOUS DISTRIBUTIONS. In C and D the nerve is in its usual position but divides before entering larynx (Lahey F H Exposure of the recurrent laryngeal nerve in thyroid operations further experiences Surg Gynec & Obst 78 239 244)

FIG 115 CAMERA LUCIDA DRAWINGS OF INTACT RAT THYROID AFTER INJECTION OF TSH (cf. Robertis) (Top left and center) Thirty min after injection of TSH Colloid particles are being extruded from cell into alveolus (Top right) Reversal of polarity 3 hrs after injection of TSH Colloid is now being resorbed. (Bottom) Six hrs after TSH Colloid is accumulating in cells and particles appear to be migrating to base of cell losing their density. This movement is thought to precede actual secretion into capillaries at base of cell. Note change in contour of cell (de Robertis E. Cytological and cytochemical basis of thyroid function Tr New York Acad Sc 50 317-335)

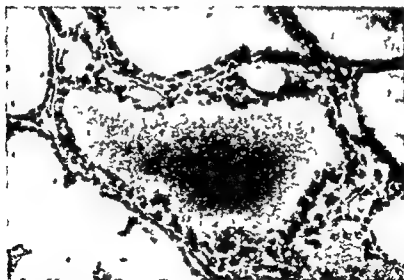
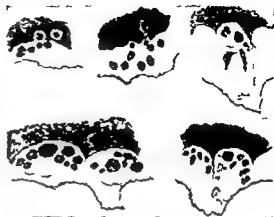


FIG 116 RADIOACTIVE IODINE IN NORMAL THYROID GLAND (See also Fig 123) Normal thyroid gland showing concentration of radioactive iodine in colloid of some follicles. This demonstration verifies the concept that under normal conditions only a few follicles are active whereas others are in a resting state. The smaller follicles are apt to show the greatest activity by a greater uptake of isotope. Note that the epithelium appears to be higher than in the adjoining follicles where little or no radioactive iodine has been deposited. (Fitzgerald, W J and Foote F W Jr The function of various types of thyroid carcinoma as revealed by the radioautographic demonstration of radioactive iodine J Clin Endocrinol 9 115-117, 1949)

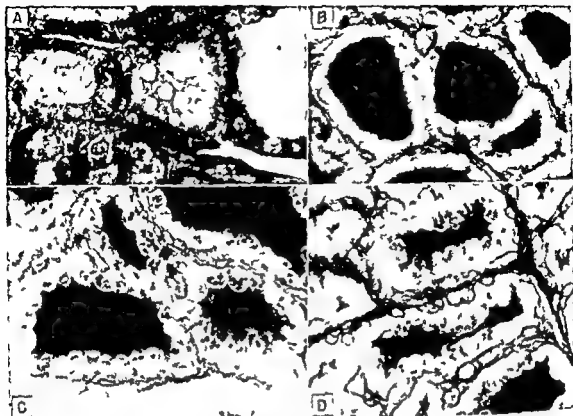


FIG 117 EFFECT OF THYROTROPIC HORMONE Effect of thyrotropic hormone on rat thyroid as well as demonstration of freezing drying fixation technic on histology of the thyroid (A) Rat thyroid Photomicrograph of section prepared by the usual methods of fixation Bensley stain (B) The same but prepared by the freezing drying technic Note absence of vacuolization which de Robertis believes is an artefact (C) The same 3 hrs after injection of TSH Note increase in particles in thyroid cells bulging of cell apices toward colloid increased height of cells and enlargement of capillaries at cell bases Resorption of colloid underway (D) The same after 10 days of daily injections of TSH Note further increase in height of cells diminishing size of colloid reservoirs increase in number as well as size of capillaries (de Robertis E Cytological and cytochemical bases of thyroid function Tr New York Acad Sc 50 31, 335)

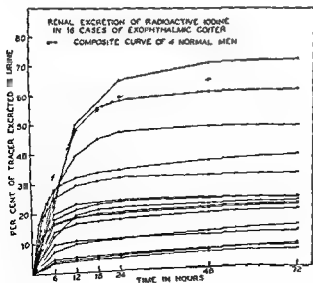


CHART 28 (Left) URINARY EXCRETION OF RADIOIODINE IN EXOPHTHALMIC GOITER Each case (total 16) varied in severity of the disease and amount of urinary radioiodine After an initial period of rapid excretion of radioiodine there is a constant slow output For comparison the composite curve of normal men is illustrated (Keating F R Power M H Berkson J and Haines S F The urinary excretion of radioiodine in various thyroid states J Clin Investigation 26 1138 1151)

CHART 29 (Right) URINARY EXCRETION OF RADIOIODINE IN MYXEDEMA Greater amounts of radioiodine are excreted in the urine of myxedematous patients (total 6) and a longer period of time is required to reach a plateau. For comparison the composite curve of normal men is illustrated (Kistling F R Jr Power M H Berkson J and Humes S F The urinary excretion of radioiodine in various thyroid states J Clin Investigation 26 1138 1151)

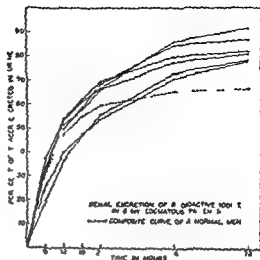


FIG 118 THIOCYANATE GOITER Histologic section showing marked hyperplasia. Myxedema may occur with such goiters (Rawson R R and McArthur J W Radioiodine its use as a tool in the study of thyroid physiology J Clin Endocrinol 7 35 263)

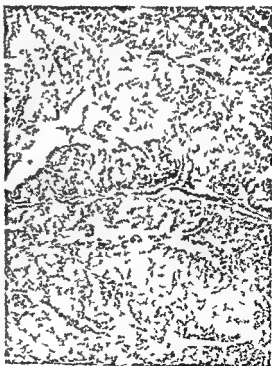


FIG 119 THIOCYANATE GOITER The same wild hyperplasia is to be seen (Rawson R R and McArthur J W Radioiodine its use as a tool in the study of thyroid physiology J Clin Endocrinol 7 235 263)



FIG 120 THYROID HYPERPLASIA IN GRAVES'S DISEASE (*Left*) Photomicrograph showing columnar epithelium in moderately active gland de Robertis considers the vacuolization an artefact i.e. not representing actual spherical entities but he admits that the occurrence of these from ordinary methods of fixation may result from a difference in the peripheral colloid as compared with the central colloid Therefore the vacuolization may represent activity as shown above in the camera lucida drawings ($\times 110$) (*Right*) Photomicrograph of early iodine effect Note cuboidal epithelium lining most alveoli ($\times 110$) (For marked involution from iodine see Fig 198 right p 480)

FIG 121 STEPS IN EXAMINATION OF THYROID GLAND (1) Position of thyroid cartilage Laryngeal prominence (Adam's apple) should be centered in plumb line through middle of face downward (2) Head turned to side (3) Thumb on thyroid cartilage displaces it to opposite side (4) Index or middle finger is behind sternocleidomastoid muscle and with thyroid cartilage displaced lobe of thyroid may be palpated if in normal position (5) The subject then swallows the examining fingers are held lightly over the area A low lying or partial sub sternal lobe (enlarged) will rise on swallowing and may be held up if thumb and finger can be pressed underneath On release the lobe may be palpated as it descends



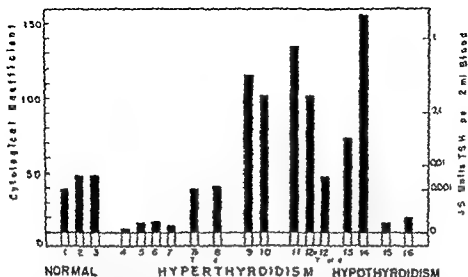


CHART 30 PITUITARY THYROID STIMULATING HORMONE (TSH) IN BLOOD OF PATIENTS WITH DIFFERENT TYPES OF THYROID DISEASE. Diagram indicating assay of thyroid stimulating hormone (TSH) in 16 human cases. On the left side cytologic coefficient (C_c) of the guinea pig thyroid (i.e. number of colloid droplets per follicle in guinea pig thyroid injected with 2 cc. of blood extract) and on the right side the corresponding concentrations of TSH (in Junkmann Schoeller units) are shown.

CASES	
1 2 3	Normal
4 5 6 7a	Untreated Graves's disease
7b	Same as 7a but after thyroidectomy
8	Graves's disease treated with thiouracil
9	Recurrent toxic goiter with severe proptosis and myxedema of the legs
10	Toxic goiter with localized edema
11 12a	Toxic goiter of the ophthalmic type
12b	Same as 12a but after treatment with thyroid
13	Spontaneous myxedema
14	Postirradiation myxedema
15	Cretinism intensely treated with thyroid
16	Primary myxedema

(de Robertis E. Assay of thyrotropic hormone. J Clin Endocrinol 8:6-956)

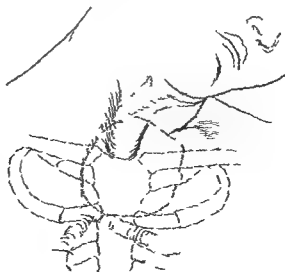


FIG 122 TRACHEAL COMPRESSION. How stridor may be produced by bending head and neck laterally when intrathoracic goiter is present.

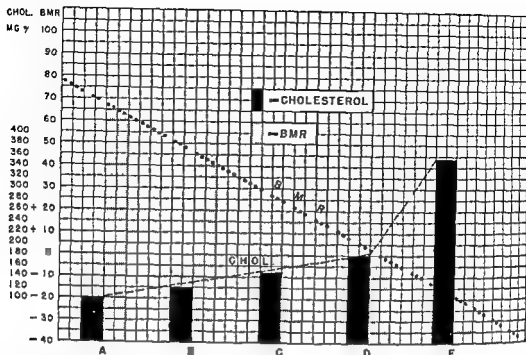


CHART 31 CHOLESTEROL Relationship between average plasma cholesterol values and average basal metabolic rates in various thyroid states (A) Severe hyperthyroidism in crisis or on verge of crisis (B) Hyperthyroidism—average of all types (C) Hyperthyroidism with adenomatous goiter (D) Normal individuals (E) Myxedema Note The sharp rise in plasma cholesterol is of more value in the diagnosis of myxedema than in hyperthyroidism

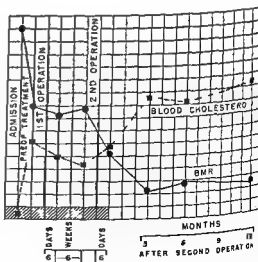
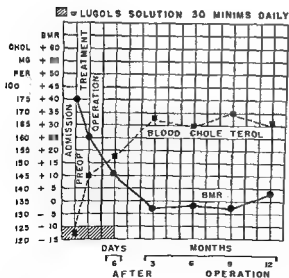


CHART 32 HYPERTHYROIDISM AND PLASMA CHOLESTEROL Averages of plasma cholesterol values and basal metabolic rates before and after subtotal thyroidectomy. Note result of hemi thyroidectomy as compared with subtotal thyroidectomy in one stage (Hurthall L M Blood cholesterol in thyroid disease II Effect of treatment Arch Int Med. 52 86 95)

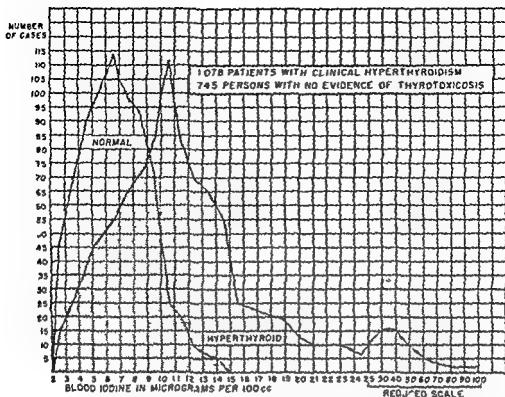


CHART 33. TOTAL BLOOD IODINE. Total blood iodine values in individuals with and without clinical hyperthyroidism. Note the overlapping. Organic or protein bound iodine should not show such wide variations because it is not easily influenced by dietary iodine (Lahey F H and Perkin H J. The level of iodine in the blood Arch Int Med 65 387 393).

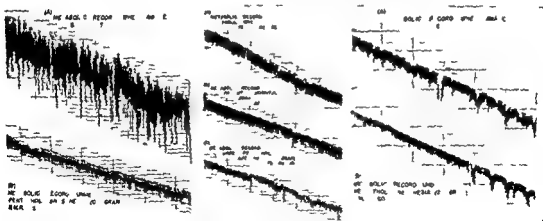


CHART 34. BASAL METABOLIC TEST RECORDS showing effect of pentothal in nervous and hyperthyroid patients.

(Left) Nervous patient (A) Awake—BMR plus 31% (B) Asleep with pentothal anesthesia (0.6 Gm)—BMR plus 5%.

(Center) Nervous patient (A) Test performed as outpatient—BMR plus 32% (B) Test performed as hospital patient—BMR plus 1% (C) Test performed under pentothal anesthesia (0.6 Gm)—BMR minus 10%.

(Right) Hyperthyroid patient (severe) (A) Awake—BMR plus 62% (B) Asleep with pentothal anesthesia (2.0 Gm)—BMR plus 60%.

(Bartels E C. Basal metabolism under pentothal anesthesia J Clin Endocrinol 9 1190-1201).

SECTION 15

ENDEMIC GOITER

I ETIOLOGY

A GENERAL INFLUENCES

- 1 Heredity—by increased susceptibility to goitrogenic factors^{10 40 47 53 56}
- 2 Geographic^{41 43 51 67}
 - a These are considered to be due to low iodine content of water and/or soil
 - b Endemic cretins are found in the following areas
 - (1) Pyrenees
 - (2) Central Alps
 - (3) Himalayas
 - (4) Carpathian Mountains
 - (5) Certain mountainous sections of Germany
 - (6) Parts of Persia
 - (7) Northwestern districts bordering Pacific Ocean (United States and Canada)
 - (8) Valleys of Sudan
 - (9) Northern Italy
 - (10) England
 - (11) Russia
 - (12) Finland
 - (13) Great Lakes
 - (14) White Mountains of New Hampshire
 - (15) Philippines⁴⁶
 - c Endemic goiter is rare in Japan⁴⁷
- 3 Infection—on account of unsanitary conditions^{15 41 43 44 60}
- 4 Goitrogenic factors—known or unknown^{2 3 7 9 11 14 17 19 23 33 35-37 41 44 48 50 54 57 61}
 - a The following produce experimental goiter but have not been proved either singly or in combination, as the cause in humans
 - b Dietary deficiencies or abnormalities⁴⁴
 - (1) Deficiency of
 - (a) Iodine
 - (b) Vitamins A B or C
 - (2) Excess of
 - (a) Fat
 - (b) Fatty acids
 - (c) Lime^{30 35}
 - (d) Proteins (as meat)

(3) The following foods may be factors⁹

- (1) Bran
- (2) Cabbage²⁸
- (3) Ground nuts
- (4) Maize
- (5) Brassica seeds
- (6) Turnips¹⁷
- (7) Rutabagas¹⁷

c Agents

- (1) Thiourea derivatives^{14 15 26 41 54}
- (2) Phenyl thiocarbamide⁴¹
- (3) Sulfamylguanidine²
- (4) Cyanates⁴⁴
- (5) Cyanides^{4 5 1}
- (6) Promizole³³

5 Combination of any or all above especially during times of increased demands of²

- a Puberty
- b Pregnancy¹⁰
- c Menopause
- d Cold¹¹

II HYPOTHETICAL MECHANISM OF DEVELOPMENT OF ENDEMIC GOITER^{34 35}

A PREMISE—Inadequate iodine metabolism or hormone synthesis

- 1 Iodine deficient water or food supply
- 2 Malabsorption of iodine by
 - a Gastro intestinal tract
 - b Thyroid gland from effect of goitrogens
- 3 Insufficient thyroid hormone synthesis due to goitrogens

B FIRST STAGE—HYPERPLASIA^{8 11 24 40}

- 1 Thyrotropic hormone production is increased by
 - a Iodine deficiency acting on pituitary cells
 - b Goitrogen
 - (1) Depriving thyroid of iodine
 - (2) Blocking thyroid hormone synthesis
- 2 Results
 - a Thyroid cell hyperplasia (overactivity)

- b Thyroid cell (or follicle) proliferation (overactivity and multiplication)
- c Deficiency of thyroid cell iodine
- d Reduced or absent hormone synthesis
- Hyperplastic hyposecretory goiter

C SECOND STAGE—COLLOID STORAGE

- 1 First stage should lead to thyroid deficiency as occurs in thouracil administration but it is assumed that variable conditions exist as
 - a Effective concentration of hypothetical goitrogens
 - b Bodily demands for thyroid hormone
 - Availability of iodine in physiologic or pharmacologic amounts
- 2 Periodical absorption of iodine at abnormal rate by hyperplastic thyroid cells

- a Absorption of iodine and colloid storage is faster than conversion of colloid to hormone because of decreased proteolytic enzymes
- b Colloid is stored i.e. colloid goiter

III THIRD STAGE—COLLOID NODULES

- 1 Irregular follicular development is aided by budding in hyperplastic stage
- 2 Another period of iodine unavailability or increased goitrogen activity is assumed
- 3 Hormone synthesis is decreased
- 4 Hyperplasia and new follicle formation occur while colloid is being slowly absorbed from the others
 - a Hormone synthesis is increased and thyrotropic hormone is suppressed causing a change in polarity
 - b Again with change in polarity by variation of conditions colloid is deposited in new or partially depleted follicles
 - c Larger acini
 - (1) Pressure is proportional to number of active cells secreting colloid
 - (2) Colloid is thus trapped more effectively
 - (3) Thyroid epithelium becomes
 - (a) Flattened
 - (b) Atrophic
 - (4) Mechanism is possibly similar to any secreting cyst

- d Atrophic epithelium surrounding colloid stimulates fibrous tissue proliferation resulting in a colloid nodular goiter

E FOURTH STAGE—Development of thyroid deficiency or excess in colloid nodular goiter can be postulated by variation of conditions which permit (see Fig 123)

- 1 Crowding out of all responsive thyroid tissue
- 2 Continuous stimulation of responsive thyroid cells to hyperthyroidism by above mechanism
 - a Within hypersecretory nodules
 - b Superimposed upon a hyperplastic goiter

III RELATION TO CRETINISM (see 24 IV, VI)

A THYROID FUNCTION

- 1 Prenatal
 - a Fetus with goiter may be stillborn
 - b Infant with goiter (large) with euthyroidism
 - c Deficiency may appear soon postnatally or much later
- 2 Postnatal—in children with goiter
 - a Responsive thyroid tissue present
 - b Less marked abnormalities than with thyro aplasia

II CHARACTERISTICS^{13, 4}

- 1 Same as in other cretins
- 2 Deaf mutism
- 3 Feeble mindedness
- 4 Idiocy
- 5 Cerebral diplegia
- 6 Tetany

C OUTCOME OF ENDEMIC CRETIN WITH GOITER

- 1 Thyroid function—when unchanged
 - a Thyroid deficiency remains
 - b Cretinous appearance maintained
 - c Mental retardation
 - (1) Marked
 - (2) Idiocy may occur depending on degree of thyroid hypofunction
 - d Slight genital development if some thyroid secretion is present
- 2 Thyroid function increasing to normal during
 - a Childhood
 - (1) Cretinous appearance may be lost

- (2) Growth at normal rate
- (3) Normal puberty and reproductivity

b Adulthood

- (1) Cretinous appearance retained

- (2) Growth absent or slightly below normal

- (3) Sexual function improves

- 3 Hyperthyroidism may develop plus findings as noted above

REFERENCES

- 1 Aron M Action de la prehypophyse sur la thyroïde chez le cobaye *Compt rend Soc de biol* 102 682 684 (Nov.) 1929
- 2 Astwood E B Chemical nature of compounds which inhibit function of thyroid gland *J Pharmacol & Exper Therap* 78 79 89 (May) 1943
- 3 Astwood E B Busell A and Hughes A M Further studies on chemical nature of compounds which inhibit function of thyroid gland *Endocrinology* 37 456 481 (Dec) 1945
- 4 Barker M H Blood cyanates in treatment of hypertension *JAMA* 106 762 767 (Mar) 1936
- 5 Barker M H Lindberg H A and Wald M H Further experiences with thiocyanates clinical and experimental observations *JAMA* 117 1591 1594 (Nov.) 1941
- 6 Baumann E J Metzger N and Marine D Mode of action of thiourea on thyroid gland of rabbits *Endocrinology* 34 44 49 (Jan) 1944
- 7 Broders A C and Parkhill E M Symposium on surgical lesions of thyroid diffuse and adenomatous goiter and goiter induced by various agents *Surgery* 16 633 646 (Nov.) 1944
- 8 Chesney A M Clawson T A and Webster B Endemic goitre in rabbits incidence and characteristics *Bull Johns Hopkins Hosp* 43 261 277 (Nov.) 1928
- 9 Crotti A Diseases of Thyroid Parathyroids and Thymus ed 3 p 550 Philadelphia Lea & Febiger 1938
- 10 de Quervain F and Wegelin C Der endemische Kretinismus p 180 Berlin Springer 1936
- 11 de Robertis H and Gonçalves J M Oxidation reduction potential of thyroid follicle in normal and experimental conditions *Endocrinology* 36 243 250 (Apr) 1945
- 12 Estes J E and Keith N M Hypothyroidism and mild myxedema from thiocyanate intoxication *Am J Med* 1 45 52 (July) 1946
- 13 Faltz W The Ductless Glandular Diseases pp 158 166 Philadelphia Blakiston 1916
- 14 Freiesleben E and Kjerulf Jensen K The effect of thiouracil derivatives on fetuses and infants *J Clin Endocrinol* 7 47 51 (Jan) 1947
- 15 Gaylord H R and Marsh M C Carcinoma of the thyroid in the salmonoid fishes An investigation and experimental study conducted jointly by the Gratwick Laboratory of the State Institute for the Study of Malignant Disease Buffalo N Y and the United States Bureau of Fisheries *Bull Bureau of Fisheries* 32 No 790 (issued April 22 1914) 1912
- 16 Goldsmith E H Gordon A S and Charipper H A Analysis of effects of continued thiourea treatment in pregnancy and on development of offspring in rat *Am J Obst & Gynec* 49 197 206 (Feb) 1945
- 17 Greer M A Ettlinger M G and Atwood E H Dietary factors in the pathogenesis of simple goiter *J Clin Endocrinol* 9 1069 1079 (Nov) 1949
- 18 Grumbrecht P and Lorser A Fruchtlos durch thyreotropes Hormon der Hypophyse *Klin Wchnschr* 17 233 235 (Feb) 1938
- 19 Halsted W S An experimental study of the thyroid gland of dogs with especial consideration of hypertrophy of this gland *Johns Hopkins Hosp Rep* 1 373-422 1896
- 20 Hercus C E and Purves H D Studies on endemic and experimental goitre *J Hyg* 35 182 203 (June) 1936
- 21 Higgins G M Study of goitre in promizole with reference to thyroid metabolism and blood Am J M Sc 210 347 362 (Sept) 1940
- 22 Higgins G M and Ingle D J Relation of hypophysis to certain changes induced in rat by goitrogen promizole *Endocrinology* 38 110 121 (Feb) 1946
- 23 Higgins G M and Joneson O R Effect of graded doses of thiouracil on experimental goiters induced by promizole *Am J M Sc* 212 294 301 (Sept) 1946
- 24 Higgins G M and Larson R A Hyperplasia of thyroid gland induced by 4,2-diaminophenyl 5 thiazolesulfone (promizole) *Proc Staff Meet Mayo Clin* 19 137 141 (Mar) 1944
- 25 Hurxthal L M and Musulin V Cretinism *Am J Med* 1 56 82 (July) 1945
- 26 Jones G E S Delfs E and Foote H C The effect of thiouracil hypothyroidism on reproduction in the rat *Endocrinology* 39 331 344 (June) 1946
- 27 Kennedy T H Thioureas as goitrogenic substances *Nature* 150 233 234 (Aug) 1940
- 28 Keston A S Goldsmith E D Gordon A S Charipper H A Effect of thiourea upon metabolism of iodine by rat thyroid *J Biol Chem* 152 241 244 (Feb) 1944
- 29 Lang Theo Bisherige Ergebnisse u meiner Messungen und Tierversuche in Hinblick auf die Radioaktivitätshypothese des endemischen Kropes und Kretinismus *Tenth Third Internat Conf Study Goiter* 1938 pp 20-30
- 30 Leatham J H Plasma protein concentrations and organ weights of rats on high protein diet *Endocrinology* 37 157 164 (Sept) 1945
- 31 Leblond C P Gross J Peacock W and Evans R D Metabolism of radio iodine in thyroids of rats exposed to high or low temperatures *Am J Physiol* 140 671 676 (Feb) 1944
- 32 Mackenzie J B Mackenzie C G and McCollum E V Effect of sultamylguanidine on thyroid of rat *Science* 94 518 519 (Nov) 1941
- 33 Marine D Physiology and principal interrelations of thyroid *JAMA* 104 2250 2255 (June) 1935

- 34 ——— The pathogenesis and prevention of simple or endemic goiter *JAMA* 104 2334-2341 (June) 1935
- 35 Marine D and Baumann E J Further studies on etiology of goiter effect of cyanides *Tr A Am Physicians* 47 261-267 (May) 1932
- 36 Marine D Baumann E J and Cipra A Studies on simple goiter produced by cabbage and other vegetables *Proc Exper Biol & Med* 26 872-874 (June) 1928 19 9
- 37 Marine D Baumann E J Spence A W and Cipra A Further studies on etiology of goiter with particular reference to action of cyanides *Proc Soc Exper Biol & Med* 29 772-775 (Mar) 1931
- 38 Marine D Baumann E J Webster B and Cipra A Occurrence of antagoistic substances in plants *J Exper Med* 57 121-137 (Jan) 1933
- 39 Marine D and Lenhart C H The pathological anatomy of the human thyroid gland *Arch Int Med* 7 506-535 (Apr) 1911
- 40 Martin L Hereditary and familial aspects of exophthalmic goitre and nodular goitre *Quart J Med* 14 20-219 (Oct) 1945
- 41 McCarrison R The Etiology of Endemic Goiter London Bols and Danielsson 1913 pp 40-115
- 42 ——— The Thyroid Gland in Health and Disease New York Wood 1917 pp 134-147
- 43 ——— The Simple Goiters London Bailliere Tindall & Cox 1913 pp 11-24
- 44 ——— Problem of endemic goitre *Brit M J* 1 31 (Jan) 1937
- 45 McCarrison R and Madhava K ■ Life line of thyroid gland *Indian M J Research (Memoir No 3)* March 1937 pp 1-378
- 46 Miller H W Hyperthyroidism in China Japan and the Philippines *China M J* 43 226-234 (Mar) 1929
- 47 Pfäundler M Endemic goiter and cretinism *Jahrb f Kinderh* 105 223-276 1914
- 48 Paghini G Radioemanazione (radon) ed alterazioni strumose della tiroide *Tr Third Internat Conf Study Goiter* 1938 pp 30-33
- 49 Rawson E W Evans R D Means J H Peacock W Lerman J and Cortell R G Action of thiouracil upon thyroid gland in Graves disease *J Clin Endocrinol* 4 111 (Jan) 1944
- 50 Rawson R W Hertz S and Means J H Thiocyanate goiter in man *Ann Int. Med* 19 829-842 (Dec) 1943
- 51 Richter C P and Chabby K H Toxic effects of bitter tasting phenylthiocarbamide *Arch Path* 33 46-57 (Jan) 1942
- 52 Robinson R W and O'Hare J P Further experiences with potassium sulfocyanate therapy in hypertension *New England J Med* 221 964-969 (Dec) 1939
- 53 Rosanoff A J and Handy L M Etiology of mongolism with special reference to its occurrence in twins *Am J Dis Child* 46 764-779 (Oct) 1933
- 54 Scott M The possible role of arsenic in the etiology of goiter cretinism and endemic deaf mutism *Tr Third Internat Conf Study Goiter* 1938 pp 34-49
- 55 Smith G ■ Fetal and maternal athyroidism *Endocrinology* 5 26-272 (July-Sept.) 1919
- 56 Wagner Jauregui J Ist das Entstehen des Kretinismus durch intrauterine Behandlung der Frucht zu verhüten? *Schweiz med Wchn* 68 246-247 (Mar) 1938
- 57 Wahlberg J Deficiency of iodine and excess of calcium within an endemic goiter area *Tr Third Internat Conf Study Goiter* 1938 pp 71-73
- 58 Wald M H Lundberg H A and Barker M H Toxic manifestations of thiocyanates, *JAMA* 112 1120-1124 (Mar) 1939
- 59 Webster B Studies in etiology and nature of simple goiter as produced experimentally in rabbits *West J Surg* 39 65-773 (Oct) 1931
- 60 Wegelin C Pathologic anatomy of endemic goitre and control of goitre in Switzerland *Internat Clin* 4 38-46 (Dec) 1916
- 61 Zondek H Diseases of the Endocrine Glands ed J Baltimore Wood 1935 p 207
- 62 *Ibid* pp 216-221

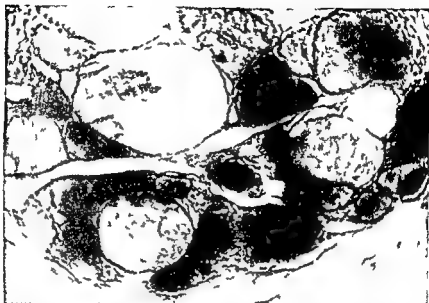


FIG 123 RADIOACTIVE IODINE IN NORMAL THYROID GLAND Normal thyroid gland showing variation in amount of radioactivity (dark areas) from follicle to follicle ($\times 160$) This evidence supports the thesis of formation of colloid or endemic goiter as outlined herein (Fitzgerald P J and Foote F W Jr The function of various types of thyroid carcinoma as revealed by the radioautographic demonstration of radioactive iodine *J Clin Endocrinol* 9 1153 1170)

SECTION 16

COLLOID GOITER

SYNONYMS

Adolescent	Simple
Early endemic	Sporadic
Iodine deficiency disease	

- | | |
|----------------------------|--|
| I DEFINITION | Uniform and variable enlargement of the thyroid gland due to an excessive colloid accumulation without gross nodular formation |
| II APPEARANCE | Normal except for goiter and unless hypothyroidism is also present (see 24 II Fig 124) |
| III AGE | In endemic areas goiter appears early in life and lasts longer majority occur about the time of puberty and diminish in size after a few years |
| IV SEX | Majority in females |
| V MENTAL DEVIATIONS | None except possibly with hypothyroidism (see 24 V 25 V) |
| VI PHYSICAL STATUS | |
| A THYROID | Enlargement may be variable uniform symmetrical or asymmetrical less firm than hyperplastic gland no bruit or thrill |
| B In toto | Normal, except with hypothyroidism (see 24 VI, 25 VI) |
| VII LABORATORY DATA | Normal findings except if associated hypothyroidism is present (see 24 VII 25 VII) |

VIII ETIOLOGY—see 15 I

IX PATHOLOGY

- | | |
|--|--|
| A Gross—Thyroid
1 Enlarged
2 Nonvascular
3 Soft
4 Cross section
a Pale
b Honeycombed
c Surface is divided imperfectly by fibrous septa | b Colloid
(1) Large amounts
(2) Thick
(3) Stains readily
(4) Iodine content decreased
2 Cells
a Flat
b Cuboidal occasionally
c Hyperplastic areas may be found
3 Stroma
a Amount decreased
b Fibrous bands are present
c Lymphocytic collections
d Hyaline degeneration
4 Glandular vascularity
a Decreased |
| B Microscopic—Thyroid
1 Follicles
a Size
(1) Variable
(2) Dilated usually | |

- b Increased—sometimes forming non toxic vascular diffuse colloid goiter

5 Changes that may develop

a Cyst formation

- (1) True cyst is of follicular origin

(a) Size—may be enormous

(b) Monolocular or multilocular

(c) Fluid is

[1] Serous

[2] Chocolate brown

(d) Cholesterol crystals may be formed

(e) Walls are

[1] Thin

[2] Thick

(2) False cyst is caused by a hemorrhage which becomes

(a) Necrotic

(b) Encapsulated

(c) Absorbed

(3) Arteries and veins may increase

b Hyperplasia with or without hyperfunction

c Malignant degeneration

d Colloid adenoma

C TYPES OF GOITER

1 Congenital

a Simple parenchymatous

(1) Colloid practically absent

(2) Large strands of cuboidal cells with abnormally large nuclei

(3) Embryonic hyperplasia probably

b Telangiectatic—hyperplasia of

(1) Large cavernous blood vessel

(2) Epithelium

c Colloid

(1) Typical colloid gland

(2) Result of iodine effect on previous hyperplasia during fetal life

2 Colloid

a Occurrence

(1) Children

(2) Young adults

b As above (1a) with euthyroidism few follicles with dark staining partly absorbed colloid

c Large follicular type with epithelium which is

(1) Pale, small

(2) Cylindrical, arranged in cushion like projections

d Small follicular

(1) Small acini amidst many epithelial cells

(2) Some undifferentiated or with hyperplasia

X SYMPTOMATOLOGY

A GENERALLY NONE

B HYPOTHYROIDISM—Varying degrees of hypofunction may be found (see 24 \IV, 25 \II)

XI DIAGNOSIS

A PHYSICAL STATUS

1 Normal except for a uniform or variable enlarged thyroid gland

2 Hypothyroidism (see 24 \IV, 25 \IV)

B LABORATORY DATA—All normal

XII DIFFERENTIAL DIAGNOSIS

—see 35 \I, \II

XIII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A SUMMARY

1 Cyst formation causes pressure if it is very large

2 Cretins may develop in severe endemic areas

3 Hypothyroidism in different degrees

4 Malignant degeneration

5 Colloid adenomatous goiter

6 Hyperthyroidism

XIV TREATMENT

A MEDICAL

1 Prophylaxis

a In endemic areas prophylactic (pharmacologic) use of iodine has reduced the incidence of simple goiter

b Results differ depending on

(1) Locality

(2) Institution of control measures

c Iodine may be derived from

(1) Dietary program

(a) Sea foods

(b) Leafy vegetables

(c) Iodized salt

(d) Balanced intake

(2) Administration of 250 gammas of iodine per day to¹

(a) Children

(b) Pregnant women

2 Desiccated thyroid—indications

a Hypothyroidism may be corrected

b Pregnant women to ensure adequate hormone supply

c Gland may shrink but this is unlikely unless accompanied by thyroid deficiency

3 Thyroid enlargement may subside with out therapy

B SURGICAL—When the goiter is large and without thyroid deficiency then subtotal thyroidectomy may be justified because of

1 Cosmetic reasons

2 Substernal extension

3 Tracheal pressure

XV PROGNOSIS

1 GENERAL

1 Little is known about outcome

2 Dependent on complications

3 General health usually good

REFERENCES

(For other references see Endemic Goiter)

1 Marine D Pathogenesis and prevention of simple or endemic goiter JAMA 104 2334 2341 (June) 1935

2 Marine D and Kimball O F The prevention of simple goiter in man J Lab & Clin Med 3 40 48 (Oct) 1917



FIG 124 COLLOID GOITER Patient with a colloid goiter before and after operation
No substernal extension Removed for cosmetic reasons

SECTION 17

NODULAR (MULTIPLE) GOITER

SYNONYMS

Nontoxic nodular goiter
Nontoxic adenoma

Multiple adenomatous goiter
Colloid adenoma

I DEFINITION

Any goiter containing multiple palpable nodules is included in this group. Single nodules are discussed under tumors of the thyroid (see 35 XI XII). At operation the latter may be a large colloid nodule in a colloid goiter with numerous smaller nodules which are not palpable.

II APPEARANCE

Normal, except goiter may be quite prominent

III AGE

After 30 years

IV PHYSICAL STATUS

A THYROID

Size variable, nodules may be small or large, soft or firm, smooth or irregular, may displace thyroid cartilage laterally, may become pendulous, enlarged neck veins in some (see Figs 125 and 126)

B IN TOTO

Normal

V LABORATORY DATA

Normal

VI ETIOLOGY—see 15 I

VII PATHOLOGY

A GROSS—THYROID

- 1 Enlargement to all degrees
- 2 Nodules are
 - a Different in
 - (1) Size
 - (2) Shape
 - b Scattered throughout the gland which has an abundance of parenchymatous tissue
- 3 Stroma
 - a Amount variable
 - b Fibrous
 - c Calcareous deposits may occur
- 4 Cross section shows encapsulated or bulging nodules with interlaced fibrous tissues
- 5 Vascular in some

B MICROSCOPIC—THYROID

- 1 Nodules
 - a Acini
 - (1) Sizes differ
 - (2) Compression near the nodules due to pressure
 - b Epithelium—flat
 - c Colloid—variable amounts
- 2 Fetal adenoma—see 35 IX A 2 b

3 Changes that may develop

- a Degeneration
 - (1) Amyloid
 - (2) Fatty
 - (3) Mucoid
 - (4) Hyaline in
 - (a) Stroma
 - (b) Perivascular areas
- b Hemorrhage into
 - (1) Adenoma
 - (2) Cyst
- c Cavernous angioma
- d Cyst in large follicle
- e Calcification

C TYPES OF GOITER

- 1 Nodular parenchymatous
 - a Large follicle or macrofollicular
 - b Small follicle or microfollicular
 - c Embryonal or trabecular with no apparent follicle formation
 - d Fetal or tubular—follicles like tubules lined with epithelium which is
 - (1) Cuboidal
 - (2) Cylindrical
- 2 Nodular colloid
 - a Papillary large follicle
 - b Simple adenoma

- 3 Diffuse and nodular
 - a Diffuse colloid plus nodular parenchymatous
 - b Diffuse colloid plus nodular colloid
 - c Diffuse parenchymatous plus nodular parenchymatous
 - d Diffuse parenchymatous plus nodular colloid
- 4 Malignant degeneration—rare (see 35 IX B)

VIII SYMPTOMATOLOGY

A GENERAL COMPLAINTS

- 1 None
- 2 Mechanical from tracheal compression
 - a Cough
 - b Dyspnea
 - c Stridor
 - d Dysphagia rarely⁶

B HYPOTHYROIDISM (see 24 XII 25 XII)

C HYPERTHYROIDISM (see 26 XII)

IX DIAGNOSIS

A PHYSICAL STATUS

- 1 Normal, except for findings in thyroid gland
- 2 Signs of
 - a Hypothyroidism
 - b Hyperthyroidism

X DIFFERENTIAL DIAGNOSIS—see 35 XI, XII

XI COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A HEMORRHAGE—Often sudden and alarming

B PRESSURE SYMPTOMS

C HYPOTHYROIDISM

D HYPERTHYROIDISM

F MALIGNANCY—From 0.5 to 17.1 per cent of all reported nodular goiters^{1-4 7 8}

G RECURRENT NODULAR GOITER

- 1 After removal of nodular nontoxic goiter recurrence is probable in due time
- 2 Greater resection may prevent this

G DEGENERATIVE CHANGES (see 2 X A 2, 4 17 VIII B 3)

XII TREATMENT

A SURGICAL

- 1 Indications
 - a Pressure symptoms
 - b Hemorrhage
 - c Malignant degeneration 3 5 8 9
- 2 Results
 - a Recurrence may slowly develop in the majority depending on
 - (1) Amount of thyroid tissue removed
 - (2) Time elapsed postoperatively
 - Regrowth occurs in variable degrees rarely with hyperthyroidism
 - Myxedema may develop

B COMPLICATIONS

- 1 Myxedema
- 2 Hyperthyroidism

XIII PROGNOSIS

A WITHOUT TREATMENT

- 1 Normal, except for enlarged thyroid gland
- 2 Complications may develop at any time (see above)

■ SURGICAL—see above

REFERENCES

- 1 Brenner H G and McKnight R ■ True adenomas of thyroid gland and their relation to cancer. *Tr Am A Study Goiter* 1940 pp 176 190
- 2 Cattell R B A more optimistic approach to cancer of the thyroid. *West J Surg* 54 444 449 (Nov.) 1946
- 3 Cole W ■ Slaughter D P and Rossiter L J Potential dangers of nontoxic nodular goiter. *JAMA* 127 883 888 (Apr.) 1945
- 4 Hinton J W and Lord J W Jr Is surgery indicated in all cases of nodular goiter toxic or nontoxic? *JAMA* 129 605 606 (Oct.) 1945
- 5 Lahey F H Carcinoma of thyroid. *Am J Roentgenol* 46 469-475 (Oct.) 1941
- 6 Means J ■ The Thyroid and Its Diseases. Philadelphia Lippincott 1937 p 602
- 7 Stout A P Tumor seminar. *Texas State J Med* 40 366 391 (Nov.) 1944
- 8 Ward R Symposium on surgical lesion of thyroid malignant goiter. *Surgery* 16 783 803 (Nov.) 1944
- 9 Warren S Classification of tumors of thyroid. *Am J Roentgenol* 46 447 450 (Oct.) 1941



FIG 125 NODULAR GOITER (*Left and center*) Age 41 female Large nodular goiter with slight substernal extension (*Right*) After removal



FIG 126 NODULAR GOITER BECOMING PENDULOUS
358

SECTION 18

INTRATHORACIC GOITER

I DEFINITION

The term intrathoracic goiter indicates an adenomatous or nodular goiter which for the most part, is entirely within the thorax. Substernal goiter indicates a goiter which has partially descended through the superior straight behind the sternum.

II APPEARANCE

Normal, occasionally swelling of face and with or without cyanosis.

III AGE

Congenital rarely average age about 40 years

IV SEX

Greater incidence in males

V PHYSICAL STATUS

A THYROID

Absent thyroid tissue in neck, inability to palpate bottom of lower poles on swallowing. Goiter may appear to be entirely in neck but have large intrathoracic extension.

B OTHER SIGNS

1 Venous distention

May be huge in neck (frog neck appearance), chest (infra red photography can easily demonstrate venous changes) upper abdomen (see Figs 127, 130 and 136)

2 Larynx

May be fixed

3 Tracheal cartilage

Displacement may be palpated

4 Demonstration of stridor

May be heard in any position which increases tracheal compression. Head is held forward, backward or turned to either side.

5 Sternum

Dullness over it on percussion, if goiter is sufficiently enlarged.

6 Color

Cyanosis rarely.

VI ROENTGENOLOGIC FINDINGS

A MISCELLANEOUS (see Figs 131, 133, 135 and 137)

1 Chest

Intrathoracic tumor is evident. Goiter may reach aortic arch rarely lower.

2 Trachea

Deviation illustrated by Bucky films taken in antero-posterior oblique lateral positions.

VII ETIOLOGY

A ENDEMIC GOITER (see 15 I)

ward through superior straight of thoracic cage

B INTRATHORACIC DESCENT OF GOITER

e Blood supply is carried along with the descending gland

1 Mechanism (see Figs 128 and 129)

2 Goiter may become fixed if it

a A goiter must be of considerable size before there is a tendency to descend

a Enlarges sufficiently

b Normal or hyperplastic glands are not apt to leave their position

b Cannot pass completely through the thoracic straight lower portion may become anchored while the upper part is too large to follow downward

c Weight of gland as well as size subject it to pressure traction from muscles of swallowing

■ Extends behind the trachea

d Direction of least resistance is down

C ABERRANT THYROID TISSUE (see Fig 134)[†]

1 Extremely rare

2 Origin from embryonic cell rests

VIII PATHOLOGY

A GROSS—see 16 VII A

II MICROSCOPIC—see 16 VII II

IX SYMPTOMATOLOGY

A HORMONAL—Thyroid function may be

- 1 Normal
- 2 Decreased
- 3 Increased

B COMPRESSION OF

- 1 Trachea
 - a Cough
 - (1) Occasionally
 - (2) Local tracheitis may cause it
 - b Paroxysmal stridor and dyspnea are due to
 - (1) Mucus in compressed portion
 - (2) Flexion of head producing increased obstruction
 - (3) Hemorrhage into adenoma
 - c Constant stridor and dyspnea are caused by
 - (1) Very narrow passage through blocked area
 - (2) Sudden increased pressure from above mentioned causes
- 2 Neck veins
 - a Sensation of congestion in the head
 - b Giddiness, especially on leaning over

C PRESSURE ON

- 1 Esophagus
 - Extremely infrequent
 - b When dysphagia is present consider
 - (1) Malignant invasion
 - (2) Plummer Vinson syndrome (atrophy of esophageal mucous membranes or esophageal webs)
- 2 Laryngeal nerves
 - a Uncommon
 - b Malignant extension usual cause

X DIAGNOSIS

A SYMPTOMATOLOGY (see above) — Complaints from compression of

- 1 Trachea
- 2 Neck veins

B SIGNS

- 1 Thyroid tissue is absent in neck
- 2 Venous distention in
 - Neck
 - b Abdomen
- 3 Stridor may be demonstrated

C ROENTGENOGRAMS

- 1 Intrathoracic tumor
- 2 Tracheal cartilage is often displaced

XI DIFFERENTIAL DIAGNOSIS

A ANEURYSM

- 1 Variable degrees of compression and displacement which may involve
 - a Trachea
 - b Mediastinum
 - Vertebrae
- 2 Pulsations are expansile under fluoroscopy examination, but unreliable because not always evident
- 3 Tracheal tug may be found
- 4 Heart examination
 - a Loud, ringing aortic second sound
 - b Harsh, high pitched systolic murmur over aneurysm
 - c Diastolic murmur may also be heard if
 - (1) Aortic ring is dilated
 - (2) Disease of aortic valves is present

5 Oblique roentgenograms may aid in diagnosis

6 Serologic tests usually positive

B ENLARGED THYMUS GLAND OR THYMIC TUMOR

- 1 Thyroid cartilage is in its normal position
- 2 If located in anterior mediastinum trachea is displaced laterally
- 3 On extension of head in children enlarged thymus rises on swallowing
- 4 Chest roentgenogram
 - a Thymus lies lower in chest and over shadows heart (covers auricles)
 - b Shape is triangular, if an enlarged gland is present
 - c Soft and regular outline
- 5 Response to roentgen therapy sometimes

C LYMPHOMAS (see Fig 137)

- 1 Lymphadenopathy elsewhere in body
- 2 Hematologic abnormalities
- 3 Chest roentgenogram
 - Thyroid cartilage in normal position
 - b Trachea is not displaced unless predominantly unilateral
 - c Bilateral often
 - d Infiltration may be extensive
- 4 Biopsy of gland
- 5 Response to roentgen therapy often

D MALIGNANT TUMOR OF LUNG

- 1 Hemoptysis
- 2 Cough is more frequent
- 3 Chest roentgenogram
 - a Mediastinal shadow may be displaced to opposite side
 - b Pleural effusion
- 4 Diagnosis may be established by
 - a Bronchoscopy
 - b Biopsy
 - c Analyses of pleural fluid for malignant cells

XII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**A SUMMARY**

- 1 Severe suffocating spells
- 2 Hemorrhage (sudden)
- 3 Circulatory embarrassment (rare)
- 4 Malignant degeneration (uncommon)
- 5 Acute infections

XIII TREATMENT**A SURGICAL**

- 1 Comment
 - a Oxygen or oxygen and helium for stridor
 - b Intratracheal intubation by anesthesiologist if necessary
 - c Removal of goiter in all cases if expedient
- 2 Operative procedure^{1 3 4}
 - a Intratracheal cyclopropane oxygen anesthesia
 - b Curved collar incision dividing platysma
 - c Raise upper flap above notch of thyroid cartilage
 - d Free sternocleidomastoid muscle on each side
 - e Bilateral high division of prethyroid muscles
 - f Ligation and division of superior thyroid vessels
 - g Division of isthmus and exposure of the trachea
 - h Ligation and division of middle thyroid veins
 - i Exposure of recurrent nerve inferior parathyroid and inferior thyroid artery if feasible at this stage

- j If not, apply traction to upper pole of the lobe and insert finger into chest behind goiter
- k Deliver intrathoracic goiter by combined upper pull and inferior pressure, decreasing transverse diameter of goiter, entering thoracic strait
- l If delivery is not accomplished
 - (1) Enter lobe in neck
 - (2) Break up and evacuate part of central portion of intrathoracic goiter
- m Deliver intrathoracic goiter now reduced in size
 - (1) Avoid injury to apical pleura
 - (2) Place moist gauze pack in thoracic space
- n Ligate inferior thyroid artery, if not already done, in continuity
- o Expose
 - (1) Recurrent laryngeal nerve in neck
 - (2) Inferior parathyroid
- p Subtotal resection of thyroid lobe including all of intrathoracic portion
- q Reconstruct remnant to trachea
- r Inspect other lobe and if indicated do subtotal resection particularly if low in position
- s Gauze pack in intrathoracic space
- t Suture prethyroid muscles
- u Close platysma and skin with clips
- v Inspect larynx and clear trachea of secretions with intratracheal catheter or bronchoscope
- 3 Postoperative complications (see Fig 138)
 - a Intrathoracic accumulation of serum
 - b Hemorrhage
 - c Infection of
 - (1) Wound
 - (2) Intrathoracic space
 - d Pulmonary infection
 - e Atelectasis

XIV PROGNOSIS**A GENERAL**

- 1 Complications may occur suddenly
- 2 Surgery can relieve
 - a Symptoms
 - b Signs

REFERENCES

- 1 Cattell R Personal communication
- 2 Colp R Substernal goitre with acute dyspnoea bronchoscopy and subtotal thyroidectomy *Ann Surg* 97 280 281 (Feb) 1933
- 3 Lahey F H Diagnosis and management of intrathoracic goiters *JAMA* 75 163 166 (July) 1920
- 4 ——— Intrathoracic Goiter *S Clin North Amer* 25 609 618 (June) 1945
- 5 Means J H The Thyroid and Its Diseases Philadelphia Lippincott 1937 p 518
- 6 Nicholson M J Anaesthesia for thyroid surgery *S Clin North America* 25 627 644 (June) 1945
- 7 Rives J D Mediastinal aberrant goiter *Ann Surg* 126 797 810 (Nov) 1947



FIG 127 INTRATHORACIC GOITER SHOWING DILATED VEINS ON UPPER CHEST



FIG 129 EXTRATHORACIC AND INTRATHORACIC NODULAR GOITER Nodular goiter which is lodged in superior strait and also intrathoracic Marked anterior and posterior trachea compression (Lahey F H and Swinton N W Intrathoracic goiter *Surg Gynec & Obst* 59 627 637)



FIG 128 NODULAR GOITER Drawing of nodular goiter with retrotracheal and substernal extension Clinically this would appear to be entirely in the normal thyroid position

FIG 130 INTRATHORACIC NODULAR GOITER
 Age 55 female Hyperthyroidism and recurrent adenomatous goiter intrathoracic Infra red photograph Adenomatous left lobe removed for hyperthyroidism Weight 128 lbs Pulse 80 BMR 1 year later—minus 17% Returned 13 years later with recurrent goiter and symptoms of mild hyperthyroidism Weight 115 lbs Pulse 86 BMR plus 15% A large intrathoracic goiter extending to ninth rib posteriorly displacing trachea to right and posteriorly Bilateral enlargement at operation almost entirely intrathoracic Most of tumor was removed by marsupialization until remaining mass could be extricated Pathologic diagnosis multiple colloid adenomatous goiter with coincident fetal adenoma Subsequent course uneventful with gain of 20 lbs in 3 months



FIG 131 INTRATHORACIC GOITER Completely intrathoracic goiter (Lahey F H Completely intrathoracic goiter Medico-Surgical Tributes to Harold Brunn Berkeley Univ California Press p 244)



FIG 132 PARATRACHEAL GOITER Para tracheal goiter with substernal extension and tracheal deviation (Jahey, P H Completely intrathoracic goiter Medico Surgical Tributes to Harold Brunn Berkeley Univ California Press p 248)



FIG 133 INTRATHORACIC GOITER Intra thoracic goiter with portion above clavicle Note marked tracheal compression Oblique view showing forward displacement and compression of trachea from retrosternal extension of goiter



FIG 134 ABERRANT INTRATHORACIC GOITER Patient had an adenoma of the thy

roid removed It was substernal in the midline and about the size of an orange A bilateral subtotal thyroidectomy was done the right lobe did not have any adenomatous changes Eleven years later a chest plate taken as a routine procedure showed a mass on the right side Patient had no symptom except moderate dyspnea The tumor was not considered to be of thyroid origin A thoracotomy and excision of the large smooth encapsulated goiter was performed It was about 10 x 15 x 10 cm in size and was situated above the hilum of the right lung in the mediastinum between the azygos vein and the superior vena cava The goiter had no connection with the neck and probably was derived from an aberrant thyroid Patient survived

FIG 135 INTRATHORACIC NODULAR GOITER
 Deviated trachea from nodular goiter partially substernal. Marked narrowing and displacement due to partly intrathoracic goiter. The position of the goiter renders it a fulcrum upon which the trachea may be compressed farther on bending head and neck laterally. This may occur during sleep causing dyspnea particularly during an acute upper respiratory infection when mucus may clog the narrowed airway.



FIG 136 INTRATHORACIC NODULAR GOITER
 WITH DILATED UPPER ABDOMINAL VEINS. Dilated veins due to superior vena cava compression.



FIG 13. INTRATHORACIC GOITER SIMULATING LAMPHOMATOUS TYPE OF TUMOR (Left)
 Age 53 Intrathoracic tumor proved to be an intrathoracic goiter. Paralysis of right vocal cord. Marked hoarseness, venous distention and cough for 3 months. No changes with roentgen therapy. On operation an adenoma arising from left lower lobe 6 m. in diameter was removed without any complications. Note tracheal displacement as shown on roentgenogram. Cricoid cartilage was in its normal position. Laryngeal paralysis remained after operation. Pathologic report: multiple colloid adenomatous goiter. (Right) Condition 4 months after operation. Recurrent laryngeal paralysis still present 18 months later.



FIG 138 INTRATHORACIC NODULAR GOITER (Top left) Intrathoracic goiter (Top right) Specimen removed (15 cm long) (Bottom) Chest roentgenogram showing extent of cavity from which goiter was removed. Space packed with gauze.



SECTION 19

THYROIDITIS ACUTE NONSUPPURATIVE AND SUPPURATIVE

I DEFINITION

- A ACUTE NONSUPPURATIVE An inflammatory process of the thyroid gland without abscess formation
- B ACUTE SUPPURATIVE Abscess may occur in normal pre existing, colloid nodules or nonsuppurative thyroiditis

II APPEARANCE

Not unusual

III AGE

Any, suppurative type more frequent in children, range from 15 to 60 years

IV SEX

Greater incidence in females

V PHYSICAL STATUS

- A THYROID Swollen, tender, overlying skin is hyperemic edematous warm to touch may be very enlarged in suppurative type

B OTHER SIGNS

- 1 Voice Hoarseness
- 2 Temperature Fever, but never very high
- 3 Muscles Flexion of neck causes muscle spasm, abdominal rigidity is rarely found in children painful swallowing

VI LABORATORY DATA

A GENERAL

- 1 White blood cells May be increased
- 2 Sedimentation rate May be increased

VII ROENTGENOGRAPHIC FINDINGS

Marked dislocation of the larynx and trachea if swelling is sufficient

VIII ETIOLOGY¹

A MICRO ORGANISMS²

- 1 Streptococcus
- 2 Staphylococcus
- 3 Pneumococcus
- 4 Bacillus coli
- 5 Bacillus typhosus
- 6 Anaerobic group

9 Puerperal infection

10 Tonsillitis

11 Typhoid

12 Pneumonia

13 Trauma

14 Pyemia

IX PATHOLOGY³

A GROSS—THYROID

- 1 Hard
- 2 Friable in some parts
- 3 Edematous
- 4 Inflammation of capsule may involve surrounding structures
- 5 Cross section
- a Red surface if late stage of disease mottled white areas
- b Fibrous tissue dense

B DISEASES

- 1 Influenza
- 2 Malaria
- 3 Smallpox
- 4 Measles
- 5 Cholera
- 6 Dysentery
- 7 Mumps
- 8 Scarlet fever

c Degenerative changes

(1) Abscesses

(2) Gangrene

II MICROSCOPIC—THYROID

1 Acini

a Normal

b Atrophic

c Destruction—suppurative type

2 Stroma

a Swollen

b Leukocytic infiltration

c Fibrous tissue abundant

X SYMPTOMATOLOGY

A GENERAL

1 Pain in anterior neck aggravated by swallowing

2 Thyroid

a Tenderness

b Visible swelling may be noted

3 Malaise

4 Fever chills rarely

5 Anorexia

6 Nausea

7 Vomiting

8 Shooting pains occasionally in

a Ears

b Occipital region

■ Lower jaw

d Shoulders

9 Laryngitis or laryngotracheitis

10 Cough

11 Palpitation

12 Roaring in ears

13 Vertigo

14 Delirium in children

XI DIAGNOSIS

A GENERAL

1 Tenderness and swelling of thyroid gland accompanied by a mild or severe systemic reaction

2 Abscess formation in suppurative thyroiditis

XII DIFFERENTIAL DIAGNOSIS

A TONSILLITIS—Examination of throat may establish the diagnosis

II CERVICAL ADENITIS—Location of glands should identify lesion

C LUDWIG'S ANGINA

1 An acute streptococcal or other infection which

a Starts in the floor of the mouth

b Spreads to jaw and down into neck

2 Tongue ■ pushed upward because of the swelling and induration ■ the floor of the mouth

D MALIGNANT GOITER (especially sarcoma)

1 Older age group

2 Surrounding tissue may be involved

XIII COMPLICATIONS
SEQUELAE AND ASSOCIATED
DISEASES

A ABSCESS FORMATION

B CELLULITIS

C SEPTICEMIA (infrequent)

D GANGRENE—Rare in nonsuppurative type

E HEMORRHAGE—Occurrence more often in suppurative thyroiditis

F MYXEDEMA (uncommon)

G ASPHYXIA (occasionally in both kinds)

H PERFORATION (once in a while) into

1 Trachea

2 Esophagus

3 Pleura

4 Mediastinal space

XIV TREATMENT

A MEDICAL

1 Trial of

a Sulfonamides

b Penicillin—infection may be resistant

c Thiouracil has been suggested⁴

d Aureomycin, streptomycin and chloromycetin have not been adequately evaluated

2 Local applications

a Early—cold compresses or ice packs

b Later—hot packs

II SURGICAL

1 Intervention at the proper time although it may be difficult to determine

2 Indications

a Abscess formation

b Probable suppuration

(1) Protracted course

(2) Increasing pain

(3) Fever

(4) Leukocytosis

(5) Enlarging gland

3 Procedure

a Incision and drainage

b Lobectomy

XV PROGNOSIS

A GENERAL

- 1 Outcome depends on severity of infection

- 2 Inflammation may
 - a Subside rapidly
 - b Develop into abscesses
- 3 Complications may respond to treatment

REFERENCES

- 1 Crotti A Diseases of the Thyroid Parathyroids and Thymus Philadelphia Lea & Febiger 1938 pp 309 311 and 313
- 2 Hertz J On Goitre and Allied Diseases Especially Thyrotoxicosis Copenhagen Munksgaard and London Oxford 1943 p 414
- 3 Hertzel A E Diseases of the Thyroid Gland New York Hoeber 1942 pp 342 343
- 4 King H T and Rosellini L J Treatment of acute thyroiditis with thiouracil preliminary report J.A.M.A. 129 267 268 (Sept.) 1945
- 5 Womack N A Symposium on surgical lesions of thyroid thyroiditis Surgery 16 10-8 (Nov.) 1944

SECTION 20

CHRONIC NONSPECIFIC THYROIDITIS

I DEFINITION

A subacute or chronic condition of the thyroid gland characterized by various histopathologic changes possibly due to inflammation. It cannot be classified as Riedel's or Hashimoto's struma.

II APPEARANCE

Same as Riedel's or Hashimoto's struma.

III AGE

Any.

IV SEX

Twenty times more frequent in females.

V PHYSICAL STATUS

A THYROID

Variable in contour and firmness, often considered adenomatous goiter or cancer of thyroid, difficult to identify before operation.

B IN TOTO

Normal or findings of hypothyroidism (rare).

VI LABORATORY DATA

Normal except when myxedema is present.

VII ETIOLOGY

A UNKNOWN

B MILD INFECTION POSSIBLY

C TRAUMA MAY BE FACTOR

VIII PATHOLOGY¹ *

A GROSS THYROID—Variable nothing characteristic

B MICROSCOPIC—THYROID

1 Epithelium—absent or mild acidophilia

2 Stroma

a Fibro is slight

b Round-cell infiltration

c Colloid pillared occasionally

IX SYMPTOMATOLOGY

A COMMON

PER CENT

1 Presence of goiter

25

2 Enlargement in neck

25

3 Pressure sensation

25

4 Hoarseness

■

5 Dysphagia

7

6 Thyroid deficiency symptoms

6

B MISCELLANEOUS

1 Nervousness

2 Fatigue

3 Cough

4 Discomfort in neck

5 Choking sensation

X DIAGNOSIS

A BIOPSY OF THYROID

1 Microscopic studies are necessary for final decision

2 Preoperative diagnosis possible in 12 per cent by elimination of other causes of thyroid enlargement

XI DIFFERENTIAL DIAGNOSIS

A HASHIMOTO'S STRUMA (see 22 VI)

1 Bilateral

2 Nonadherent

3 Not hard

4 Pressure effects less marked

5 Biopsy diagnostic

B RIEDEL'S STRUMA (see 21 VI)

1 Unilateral often

2 Adherent to surrounding tissues

3 Hard

4 Pressure changes are more frequent

5 Biopsy diagnostic

C NODULAR GOITER (see 17 VI)

1 Nodules more discrete

2 Nonadherent

3 Fewer pressure effects

4 Biopsy diagnostic

D INVOLUTED HYPERPLASTIC GLAND

1 Previous or associated hyperthyroidism

2 Nonadherent

3 Pressure effects absent

E MALIGNANT DISEASE (see 35 XI)

- 1 Pre existing lump in neck
- 2 Growth is rapid
- 3 Adherent
- 4 Firm or hard
- 5 Biopsy diagnostic

F OTHER THYROID DISEASE (see 23)

- 1 Amyloid
 - a Chronic sepsis present elsewhere
 - b Biopsy
- 2 Tuberculosis—biopsy
- 3 Syphilis
 - a Serology positive
 - b Biopsy
 - c Response to treatment

XII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**A TRACHEAL NARROWING (rare)****B MYXEDEMA****XIII TREATMENT****A SURGICAL**

- 1 Indications
 - a Diagnosis
 - b Pressure symptoms, if not functional
- 2 Postoperative complications
 - a Tetany is rare
 - b Myxedema in 50 per cent

XIV PROGNOSIS**A GENERAL OUTCOME**

- 1 Unknown
- 2 Myxedema in some

REFERENCES

- 1 Crile G Thyroiditis Ann Surg 127 640 644 (Apr) 1948
- 2 Marshall S F Meissner W A and Smith D C Chronic thyroiditis New England J Med 238 758 766 (May) 1948

FIG 139 NONSPECIFIC TYPE OF CHRONIC THYROIDITIS This type does not conform to Riedel's or Hashimoto's thyroiditis. There are beginning scar tissue strands and follicles are disappearing. Inflammatory reaction occurs around the spilled colloid (x 29) (Marshall S F Meissner W A and Smith D C Chronic thyroiditis New England J Med 238 758 766)



SECTION 21

RIEDEL'S STRUMA^{12 11 13}

SYNONYMS

Chronic fibrous type	Ligneous goiter (chronic ligneous thyroiditis)
Woody thyroiditis	Thyroiditis simplex
Iron hard strumitis	Chronic nonsuppurative thyroiditis

✓ I DEFINITION

A specific type of thyroiditis characterized by replacement of normal follicles by dense fibrous connective tissue.

II APPEARANCE

Normal individual or may have myxedema (rare)

III AGE

Peak of incidence in fourth decade, range from second to seventh decades

/ IV SEX

Females and males equally affected according to some, while others report females involved three times as frequently as men^{14 10}

✓ V PHYSICAL STATUS

A THYROID

- ✓ Enlarges rapidly seldom as large as a goose's egg unit
- ✓ lateral involvement often suggesting focal character
- ✓ bilateral occasionally / very hard / smooth surrounding
- ✓ tissues are invaded causing fixation sometimes painful
- ✓ Normal or findings of hypothyroidism (unusual)

B IN toto

/ VI LABORATORY DATA

Normal except if myxedema is present

✓ VII ROENTGENO

GRAPHIC FINDINGS Trachea may show compression

VIII ETIOLOGY

A UNKNOWN

B THEORIES

- ✓ 1 Perithyroiditis causes partial constriction of the vessels entering the thyroid gland¹²
- ✓ 2 Lesion of inflammatory type due to previous upper respiratory or dental infection

IX PATHOLOGY^{14 8 11 15}

A CROSS—THYROID

- ✓ 1 Hard
- ✓ 2 Fibrous
- ✓ 3 Cut surface
 - a Dry
 - b White or pinkish white
 - c Bloodless
 - d Creaking sound on sectioning
 - Pseudolobulations absent

✓ Extrathyroidal involvement

B MICROSCOPIC—THYROID

- ✓ 1 Picture of chronic inflammation
- ✓ 2 Early stage (subacute)
 - a Lymphoid masses are scattered throughout gland
 - b Active fibrosis
 - c Few normal acini
 - d Numerous round cells
 - e No lymph follicles
- ✓ 3 Late stage (chronic)
 - a Lymphocytes replaced by dense sclerotic tissue
 - b Large keloidlike bundles with few spindle form cells
 - c Small vessels surrounded by round cells
- ✓ 4 Final stage (healed)—fibrous tissue with few nuclei

X SYMPTOMATOLOGY

A GENERAL

- ✓1 Sudden enlargement in normal thyroid
- ✓2 Pressure effects on the trachea and the esophagus
 - a Discomfort in neck
 - b Choking sensation
 - c Dysphagia (rare)
 - d Cough
 - e Nocturnal asthma
- 3 Dyspnea is unusual
- 4 Painful sometimes
- 5 Voice may be affected, unilateral vocal cord paralysis occasionally
- 6 Mild hypothyroid complaints in a few cases
- 7 Nervousness
- 8 Fatigue

XI DIAGNOSIS

A GENERAL

- 1 Thyroid is
 - a Very hard (woody)
 - b Smooth
 - c Involved
 - (1) In toto
 - (2) Unilaterally most often
 - d Symmetrical¹
 - e Normal in outline⁶
- 2 Preoperative diagnosis possible in 56 per cent¹⁰
- 3 Biopsy of gland

XII DIFFERENTIAL DIAGNOSIS

A HASHIMOTO'S STRUMA (see 22 VI)

- 1 Thyroid is not as hard as in Riedel's struma
- 2 Bilateral involvement
- 3 Not adherent to surrounding tissue
- 4 Nodular surface
- 5 Pressure changes rarely develop
- 6 Females are more often affected
- 7 Occurrence later in life
- 8 Myxedema commoner

B CHRONIC NONSPECIFIC THYROIDITIS—see 20 X

C CARCINOMA (see 35 VI)

- 1 Primary malignancy
- 2 It may be difficult to distinguish clinically
- 3 Biopsy is diagnostic

XIII COMPLICATIONS
SEQUELAE AND ASSOCIATED DISEASES

A TRACHEAL INVOLVEMENT ✓

- 1 Obstruction
- 2 Compression
- 3 Tracheotomy may be necessary

✓B MYXEDEMA—Occurrence in 1 per cent of cases

XIV TREATMENT

✓A SURGICAL⁷

✓1 Procedure

- a Gland is difficult to remove because of adherence to surrounding structures
- b Wedge shaped piece may be excised over trachea to relieve compression

✓2 Postoperative complications

- a Tetany
- b Recurrent nerve injury
- c Edema of trachea, temporary tracheotomy may be required

✓3 Results

- a Recurrence is possible
- b Myxedema

✓B ROENTGEN

- 1 Indication—may be effective only in early stages¹ & 18 17
- 2 Radium has been tried¹

XV PROGNOSIS

A GENERAL OUTCOME

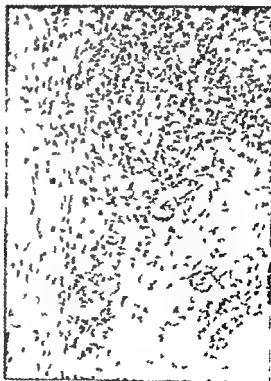
- 1 Entire gland may be destroyed if process continues
- 2 Myxedema

REFERENCES

- 1 Bayou Ueber die Thyreoiditis simplex und ihre Folgen Zentralbl f allg Path u path Anat 15 737 749 1904
- 2 DeCoursey J L New theory concerning etiology of Riedel's struma Surgery 12 754 767 (Nov) 1942
- 3 — Penthyroiditis distinct entity JAMA 123 397 399 (Oct) 1943
- 4 Graham A Riedel's struma in contrast to struma lymphomatosa (Hashimoto) West J Surg 39 681 689 (Sept) 1931
- 5 Joll C A Pathology diagnosis and treatment of Hashimoto's disease (struma lymphomatosa) Brit J Surg 27 351 359 (Oct) 1939
- 6 Lahey F H Thyroiditis its differentiation from malignancy Lahey Clin Bull 3 194 196 (Jan) 1944

- 7 ——— Thyroiditis: operative procedure for relief of tracheal constriction due to thyroiditis. *Surg. Gynec. & Obst.* 60 969-970 (May) 1935
- 8 Lee J C Chronic non-specific thyroiditis. *Arch. Surg.* 31 982-1012 (Dec.) 1935
- 9 Maloney J J Ligneous thyroiditis (Riedel's disease). *J. Med.* 10 586-599 (Feb.) 1930
- 10 Marshall, S F., McInner W A., and Smith D C Chronic thyroiditis. *New England J. Med.* 238 53-66 (May) 1948
- 11 McClintock, J C., and Wright A W Riedel's struma and struma lymphomatosa (Histiocytoma) comparative study. *Ann. Surg.* 106 11-32 (July) 1933
- 12 Renton, J M., Charters, A A., and Herne J F Riedel's thyroiditis and its treatment by radium. *Brit. J. Surg.* 26 54-60 (July) 1938
- 13 Riedel B M C L Die chronische zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse. *Verhandl. d. deutsch. Gesellsch. f. Chir.* 25 101-105 (May) 1876
- 14 ——— Vorstellen eines Kranken mit chronischer Strumitis. *Verhandl. d. deutsch. Gesellsch. f. Chir.* 26 12-129 (Apr.) 1877
- 15 ——— Leber Verlauf und Ausgang d. r. Strumitis chronica. *München med. Wchnschr.* 57 1945-1910
- 16 Schellm J A Struma lymphomatosa struma fibrosa and thyroiditis. *Surg., Gynec. & Obst.* 81 33-50 (Nov.) 1945
- 17 Watschel, K. Ueber einen Fall von eisenharter Strumitis. *Beitr. z. klin. Chir.* 67 590-603 1910
- 18 Womack, V A Thyroiditis. *Surgery* 16 9-12 (Nov.) 1944

FIG 140 RIEDEL'S STRUMA Scar tissue makes up most of gland. Few follicular remnants. Numerous round cells and scattered lymphocytes (x 100)



SECTION 22

HASHIMOTO'S STRUMA¹

SYNONYMS

Chronic lymphoid type
Struma lymphomatosa

Lymphadenitis (Joll)
Lymphadenoid goiter

✓ I DEFINITION

A specific type of thyroiditis which is characterized by lymphatic infiltration of the parenchyma and eventually by fibrosis

II APPEARANCE

Normal individual except for enlargement of thyroid gland ✓ Hypothyroidism occasionally, and hyperthyroidism rarely

III AGE

Peak of incidence in fifth decade but may occur from second to seventh decades^{2 7 10}

IV SEX

Females predominate uncommon in males^{3 10 11}

V PHYSICAL STATUS

A THYROID

Normal contour, enlarges very gradually, ✓ bilateral involvement, may surround trachea, may be smooth or ✓ nodular never very hard ✓ adjoining tissues are not affected

B LYMPH GLANDS

✓ Normal

VI LABORATORY DATA ✓ Normal, but basal metabolic rate may be elevated

VII ROENTGENO

GRAPHIC FINDINGS ✓ Tracheal narrowing may be demonstrated⁸

VIII ETIOLOGY

A UNKNOWN

✓ 1 Fibrous tissue forms pseudolobules

✓ B THEORIES

8 Colloid material

1 Early stage of Riedel's struma^{2 4}

a Scant

2 Dietary deficiency¹¹

b Absent

9 ✓ Cut surface

IX PATHOLOGY^{10 11 12 13}

A GROSS—THYROID (see Fig 143)

a Meaty appearance

b Yellowish white or pale pink

c Trabeculated

d Uniform

✓ 1 Size—enlarged moderately

2 'Circular' form of goiter common

✓ 3 Consistency

a Hard

b Rubbery

✓ 4 Muscular or fascial tissue are not adherent

✓ 5 Capsule

a Thickened

b Freely movable

✓ 6 Color

a Whitish gray

b Yellowish pink

B MICROSCOPIC—THYROID

1 Acini (see Figs 141 and 142)

✓ a Totally destroyed

✓ b Atrophied

c Variable

(1) Size

(2) Shape

✓ d Colloid

(1) Absent

(2) Scant

✓ 2 Epithelium

a Flat or low columnar, according to amount of colloid

- ✓ b Atrophy
- c Hyperplasia occasionally
- d Clumps
- ✓ e Acidophilia marked
- f Nucleus
 - (1) Basal in tall cells
 - (2) Central in flat cells
- g Mitoses absent
- h Mitochondria
 - (1) Absent
 - (2) Few in number
- ✓ i Stroma
 - a Lymphocytic infiltration may destroy acini
 - b Interstitial fibrosis in variable degrees
 - c Colloid rarely spilled
 - d Blood vessels are not affected

X SYMPTOMATOLOGY

A GENERAL

- ✓ 1 Complaints chiefly related to pressure (although not marked)
 - a Dyspnea with exertion or rest
 - b Choking sensation
 - c Dysphagia (infrequent)
- ✓ 2 Fatigue
- ✓ 3 Weight gain
- ✓ 4 Thyroid gland enlarges gradually
- ✓ 5 Hypothyroidism
- ✓ 6 Hyperthyroidism may be found in early stages
- 7 Duration of complaints¹³
 - a Average—5 years
 - b Range—9 months to 25 years

XI DIAGNOSIS

A GENERAL

- 1 Occurrence—females usually over 40 years
- 2 Symptomatology
 - a None, except that of mild pressure sometimes
 - b Myxedema occasionally
 - c Differentiate from globus hystericus
- 3 Thyroid gland should be
 - a Symmetrically enlarged
 - b Moderately hard
 - c Freely movable
 - d Nonpainful
 - e Nontender
 - f Biopsied
- 4 Preoperative confirmation is possible in 17 per cent or more

XII DIFFERENTIAL DIAGNOSIS

A RIEDEL'S STRUMA—see 21 \I

B NONSPECIFIC THYROIDITIS (see 20 \I)

- 1 Absence of specific features of other forms of thyroiditis
- 2 History of acute thyroiditis (occasionally)
- 3 Biopsy

C MALIGNANCY (see 35 \I)

- 1 Occurrence in older age group usually
- 2 Surrounding tissues may be involved
- 3 All parts of thyroid are not affected
- 4 Often diagnosis may be dependent on gross and/or microscopic examination of tissue

XIII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

✓ A MYXEDEMA

- 1 Development gradual
- 2 Present in 8 per cent

✓ B TRACHEAL PRESSURE—Rarely of great clinical importance i.e., requiring tracheotomy

XIV TREATMENT

A SURGICAL

1 Indications

- a Pressure symptoms if sufficient, justify removal of isthmus
- b If malignancy is suspected
- 2 Postoperative complications (unusual)
 - a Hoarseness may persist for months
 - b Injury to
 - (1) Recurrent nerve
 - (2) Parathyroids

3 Results

- a Recurrence is uncommon
- b Myxedema

B MEDICAL—Thyroid deficiency (see 25 \VI)

✓ C ROENTGEN OR RADIUM^{14 15}

- 1 Some recommend it
- 2 Gland must be biopsied first
- 3 Results have been good

XV PROGNOSIS

A PROGRESSIVE DISEASE

- 1 Process gradually can destroy entire gland causing hypothyroidism
- 2 Malignant degeneration does not follow¹
- 3 Myxedema

REFERENCES

- 1 Clute H M Lcker on I H and Warren S Clinical aspects of struma lymphomatosa (Hashimoto) Arch Surg 31 419 428 (Sept) 1935
- 2 Eisen D Riedel's struma with report of 7 cases Canad M A J 31 144 147 (Aug) 1934
- 3 ——— Relationship between Riedel's struma and struma lymphomatosa (Hashimoto) Canad M A J 31 147 150 (Aug) 1934
- 4 Ewing J Neoplastic Diseases ed 3 Philadelphia Saunders 1928 pp 961 962
- 5 Graham A Riedel's struma in contrast to struma lymphomatosa (Hashimoto) West J Surg 39 681 689 (Sept) 1931
- 6 Hashimoto H Zur Kenntnis der Lymphomatösen Veränderung der Schilddrüse (Struma Lymphomatosa) Arch f Klin Chir 97 219 248, 1912
- 7 Joll C A Pathology diagnosis and treatment of Hashimoto's disease (struma lymphomatosa) Brit J Surg 27 351 389 (Oct) 1939
- 8 Kearns J L Jr Struma lymphomatosa (Hashimoto) report of 2 cases Ann Surg 112 421 425 (Sept) 1940
- 9 Isahy F H Thyroiditis operative procedure for relief of tracheal constriction due to thyroiditis Surg Gynec & Obst. 60 969 970 (May) 1935
- 10 Lee J E Chronic nonspecific thyroiditis, Arch Surg 31 982 1012 (Dec) 1936
- 11 McCarroll R Note on experimental production of lymphadenoid goitre in rats Brit M J 1 5 6 (Jan) 1929
- 12 McClintock J C and Wright A W Riedel's struma and struma lymphomatosa (Hashimoto) comparative study Ann Surg 100 11 32 (July) 1937
- 13 McSwain B and Moore S W Struma lymphomatosa Hashimoto's disease Surg Gynec. & Obst 76 562 569 (May) 1943
- 14 Renton J M Charteris A A and Heggie J F Riedel's thyroiditis and its treatment by radium Brit J Surg 26 54 70 (July) 1938
- 15 Schilling J A Struma lymphomatosa struma fibrosa and thyroiditis Surg Gynec. & Obst. 81 533 550 (Nov) 1945
- 16 Womack N A Thyroiditis Surgery 16 173 782 (Nov) 1944

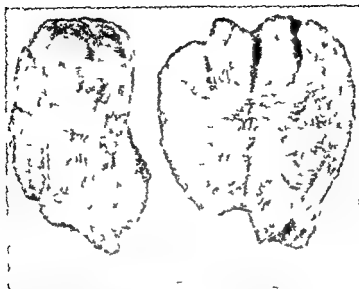


FIG 141 HASHIMOTO'S STRUMA Small lobulations due to lymphoid infiltration. Specimen 11 x 12 cm. (See low power microscopic view in Figure 142.)



FIG 142 HASHIMOTO'S STRUMA
Microscopic section (x 29)



FIG 143 HASHIMOTO'S STRUMA Few follicles present without colloid. Majority of cells are lymphocytes (x 300)

SECTION 23

INFECTIOUS GRANULOMATA

I TUBERCULOSIS^{1 4 6}

A SUMMARY

- 1 Occurrence—extremely rare
- 2 Diagnosis is usually made by histologic examination
- 3 Miliary type is more frequent than the caseous form
- 4 If recognized irradiation is advisable

II SYPHILIS^{3 4}

A SUMMARY

- 1 Occurrence—uncommon
- 2 Diagnosis is usually made by histologic examination

- 3 Development during secondary stage gummata are rare
- 4 No clinical importance as regards thyroid
- 5 Tracheal compression may occur
- 6 Antiluetic treatment indicated

III AMYLOIDOSIS⁷

A SUMMARY

- 1 Occurrence—extremely rare
- 2 Etiology as for amyloidosis elsewhere
- 3 Thyroid gland
 - a Consistency—abnormal
 - b Enlarged

REFERENCES

- 1 Coller F A and Huggins C B Tuberculosis of thyroid gland *Ann Surg* 84 804 820 (Dec) 1976
- 2 Crotti A Diseases of the Thyroid Parathyroid and Thymus Philadelphia Lea & Febiger 1938 pp 323 327
- 3 *Ibid* pp 327 334
- 4 Hertz J On Goitre and Allied Diseases especially Thyrotoxicosis Copenhagen Munksgaard London Oxford 1943 pp 419-4 0
- 5 Hare H F and Simpson H N Tuberculosis of the thyroid gland report of two cases, *Lahey Clin Bull* 2 123 126 (Apr) 1941
- 6 Klassen K P and Curtis G M Tuberculous abscess of the thyroid gland *Surgery* 17 551 559 (Apr) 1945
- 7 Walker G A Amyloid goiter *Surg Gynec & Obst* 75 374 378 (Sept) 1942

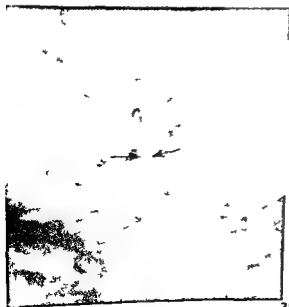


FIG 144 SYPHILIS OF THYROID Age 49 female Syphilis of thyroid causing tracheal compression and stridor Thyroid gland is hard and fixed Response to antiluetic therapy and widening of compressed area to two thirds normal lumen in 1 year No biopsy Positive Wassermann Treated with iodobismuth

SECTION 24

CRETINISM

SYNONYMS

Endemic cretinism
Congenital athyrosis
Thyro aplasia

Sporadic cretinism
Infantile myxedema
Childhood myxedema

I DEFINITION

The term 'cretinism' as used here includes the various types of thyroid deficiency which are listed above as synonyms⁴⁶ Thyroid hypofunction occurring late in pre-natal life or during the post-natal growth period which is of sufficient degree and duration, results in characteristic physical and mental changes The condition may be associated with goiter so that return of normal thyroid or excess thyroid hormone secretion may occur when goiter or responsive thyroid tissue is not present spontaneous recovery is impossible

II APPEARANCE

Dull stupid expression depression of the base of the nose, puffiness and wrinkled skin about the eyes thick tongue pot belly retarded growth and development Abnormalities depends on age of onset and duration of thyroid deficiency (see 15 III Figs 145 and 146)

III AGE

Begins in *intra uterine* life infancy childhood or puberty

IV SEX

No predominance

V MENTAL DEVIATIONS

A INTELLIGENCE

May be retarded or only subnormal, depending on age of onset duration and therapy idiots not uncommon^{11 32 60 71}

B RESPONSIVENESS

Dull slow hypokinetic rarely exceptions (see Fig 153)

C OTHER ABNORMALITIES

Lethargy or sleepiness very little irritability emotional level low, abnormally quiet

VI PHYSICAL STATUS

A NUTRITION

Malnourished rarely

1 Weight

Increased but variable

2 Fat distribution

Excessive amounts about face nape of neck supraclavicular region hips mons veneris back of hands and pot belly, may not have unusual findings (see Fig 146)

B HEIGHT

Almost always below normal depending on duration of disease therapy and family height (see Prognosis and Therapy)

C EXTREMITIES

1 Upper

Proportionate to height in nervous type right angle flexion of upper limbs⁴⁶

a Hands

Stubby spatulate pudgy in older cases (see Fig 147)

b Fingers

Stubby

c Span

Normal

2 Lower	Not remarkable, proportionate to height, knock knee or widely separated in 'nervous type' ⁴¹
a Feet	Flat feet in some
b Toes	As fingers
D SPINE	Normal or scoliosis possible, lordosis common
E INTEGUMENT	
1 General	
a Texture	Scaling coarse nonpitting edema, wrinkled (see Fig 169, p 421)
b Temperature	Decreased, may feel cool to touch
c Moisture	None
d Eruptions	Not usual, eczema in some
e Pigmentation	Cafe au lait occasionally general or patchy
f Color	Pale, slight yellowish tinge cheeks may be pink
2 Hair (see Figs 148 and 149)	
a Head	Dry fine, brittle
b Facial	Little change, may be increased at hairline eyebrows very scant
c Axillary	May be absent
d Pubic	Absent usually
e Body	Normal but may be increased ⁴²
F HEAD	
1 Shape and size	Foreshortened naso occipital diameter
2 Facial expression	Dull monkey face'' whimsical, grimaces occasionally morose
3 Eyes	
a General	Turkiness about eyes palpebral fissures may be narrowed pig eyed nystagmus with nervous type'' ⁴³ internal strabismus ⁴⁴ (see Mongolism 94 VIF 3)
b Fundi	Normal
c Visual	Normal
(1) Fields	Normal
(2) Acuity	Normal
4 Ears and nose	Deafness may occur ''depression of nasal base
5 Mouth and throat	
a General	Tongue often large and protruding, may drool lips are thick palate narrow and vaulted
b Teeth	Deciduous teeth retained late causing delayed eruption of permanent teeth resistant to caries, ridging ⁴⁵ ''
c Larynx (voice)	Hoarse often rasping
G NECK	
1 General	Not unusual appears short and thick
2 Thyroid	Normal not palpable or goiter of various sizes often tremendous nodular soft or firm tracheal compression or deviation may occur may be wholly or partially intra thoracic (see Fig 146)
H CHEST	Normal breathing may be very slow or stridulous
I HEART AND PERIPHERAL VESSELS	
1 Heart	Not usually remarkable may show enlargement and rarely evidence of congestive failure ⁴⁶
2 Rate and rhythm	Normal but bradycardia usual

3 Blood pressure	Variable often normal or slightly decreased pulse pressure
4 Peripheral arteries and veins	Slow (NOTE children's rate always higher than adults)
5 Vasomotor	Retarded or sluggish response
J BREASTS	
1 Male	Normal
2 Female	May appear normal, but without postpuberal areolae
K ABDOMEN	Protuberant
1 Liver	Normal rarely enlarged ³³
2 Spleen	Normal
3 Hernia	Umbilical common ²³
4 Tumor	None
L GENITALIA	
1 Male	
a Penis	Not fully developed unless recovery of thyroid function occurs rarely excessive size ⁵¹
b Testes	Development or descent may be dependent on recovery of thyroid function
c Prostate	Development dependent on same factor (see also result of treatment)
2 Female	
a External	Underdeveloped
b Internal	Underdeveloped
M NEUROMUSCULAR	
1 Muscles	Some hypotonicity
2 Gait	Delayed walking, clumsy waddling in "nervous cretinism" stiff gait may ambulate on their toes with "bobbing" motion some cannot walk or stand ⁴⁶
3 Body movements	Slow in "nervous cretinism" spasticity of both extremities (due to tetany) ⁴⁶
4 Tremor	None
5 Paresthesias	None
6 Reflexes	Normal or very sluggish increased in nervous type
N SPEECH	Drawl may stutter, or mute ⁴

VII LABORATORY DATA

A URINARY FINDINGS

1 General	Normal
2 Special chemical analyses (see 25 VII A 2)	
a Sugar	Absent
b Albumin	May be present
c Nitrogen	Decreased ⁵⁴
d Creatine	Absent or diminished ^{46 49 51 52 53 54 55 56 57}
e Creatinine	Normal or may be considered low for skeletal age ^{50 79}
f Sodium	As in myxedema
g Potassium	As in myxedema
h Calcium	As in myxedema ⁵⁴
i Phosphorus	As in myxedema ⁵⁴
j Chlorides	Normal or decreased ¹⁷
k Iodine	Decreased ²³

B HEMATOLOGY

1 Red blood cells	Normal or decreased
2 Hemoglobin	Normal or slightly decreased

3 White blood cells	Normal or slightly decreased
4 Differential	Decreased polymorphonuclear neutrophils increased monocytes or eosinophils but of no clinical importance
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal (but low average)
2 Nonprotein nitrogen	Normal, increased rarely ³²
3 Protein (plasma)	Normal or increased to 8 or 8.5 Gm % ^{33 41}
a Albumin	Normal
b Globulin	Increased
c Beta globulin	Increased (compared with adult standards)
d Gamma globulin	Increased (compared with adult standards)
e A/G ratio	Reversed
f Fibrinogen	Normal
4 Uric acid	Normal or decreased ³⁴
5 Cholesterol	Increased usually ^{4 33 40 47 68}
6 Sodium	Normal
7 Potassium	No data
8 Calcium	Normal
9 Phosphorus	Decreased ⁷
10 Chlorides	Normal
11 Phosphatase	Decreased ^{30 40 64 66}
12 Iodine	Low total and plasma bound ^{30 40 64}
13 Creatine	Decreased
14 Creatinine	No data
15 Magnesium	Probably as for myxedema
16 Lipids (serum)	Increased ³¹
D FUNCTION TESTS	
1 Tolerance	
a Glucose	
(1) Oral	Variable results ^{14 4 47 61}
(2) Intravenous	Decreased
b Glucose insulin	Increased sensitivity
c Insulin	Increased sensitivity
d Iodine	Decreased
e Creatine	Increased or decreased for chronologic age, but normal for skeletal age ^{3 60 7}
2 Adrenal water	Normal
3 Salt deprivation	Normal
4 Balance	
a Nitrogen	Positive (on initial therapy—negative balance, later increased—see Chart 38) ^{31 36 4 60}
b Calcium	Positive
E MISCELLANEOUS	
1 Basal metabolic rate	Usually low unless spontaneous improvement in cretinism with goiter (see below)
2 Circulation time	No data—see 25 VII E 2
3 Sedimentation rate	Normal
4 Specific dynamic action of protein	See 25 VII E 4
5 Gastric analysis	See 25 VII E 5
6 Electrocardiogram	T waves variable ³⁶
7 Blood volume	Decreased

8 Electroencephalogram	Fewer alpha waves than normal ⁷ brain metabolism retarded ²¹
F URINARY HORMONE ASSAYS	
1 FSH	Normal or rarely positive ²²
2 LH	No data
3 Estrogens	Decreased
4 Pregnanediol	Negative
5 17 ketosteroids	Decreased, about 2 to 4 mg/24 hrs ^{4 63 71}
6 11 oxysteroids	No data
7 Achheim Zondek	Negative
8 TSH	Positive, ⁶⁴ but results variable may remain slightly positive even after treatment
G BIOPSY	
1 Endometrial	No data could be normal occasionally
2 Testicular	Variable may be normal
H VAGINAL SMEAR	Normal or hypoestrogen effect
I SEMEN ANALYSIS	Decreased count ³

VIII ROENTGENOLOGIC FINDINGS

A SKULL (see Fig 154)	
1 Cranial vault	Increased density ²⁰ late closure of fontanelles cranial base shortened developmental deficiency lies in occipital parietal bones and a little in the frontal area sphenoid occipital synchondrosis causes 'monkey face'
2 Sella turcica	Enlarged (see 2 XIV G 5a)
3 Mandible	Normal may be retarded ⁷⁰
4 Sinuses	Normal some small
5 Teeth	Retained deciduous teeth ^{70 68 71}
B EPIPHYSEAL STATUS (bone age)⁶⁰	
1 At birth or during first year of life in congenital athyroidosis	Fetal stage shown by absence of centers of ossification in pelvis and lower end of femur
2 Older children	A lag of 10 years or more depending on the duration of the disorder before treatment
3 If within 2 years of its onset	Normal limits although often on the low side
4 Previously treated cases	May not be retarded
5 With goiter and return of normal thyroid function	Chronologic age may be approached
C LONG BONES	Thickened cortices radii are shorter than average ⁸⁰
D VERTEBRAE	Development delayed
E BONE TEXTURE	
1 General	Coarse trabeculae
2 Osseous centers	Retarded development fragmented appearance ⁰
3 Cartilages	Multiple irregular islets of ossification which enlarge to form spongy, porous fluffy masses all centers of endochondral ossification may be affected, osteochondritis common (see Fig 156) ^{1 19}
4 Epiphyses	Dysgenesis often present delayed bony union of epiphysis and diaphysis plate hard densely calcified (see Figs 150 and 155) ^{13 15 23 29 4 70 77 80}

F MISCELLANEOUS

- | | |
|-----------|--|
| 1 Trachea | May be compressed in any direction by large goiter |
| 2 Chest | Heart size normal or enlarged |

IX ETIOLOGY

A PRENATAL

- 1 Congenital
 - Athyrosis—there may be germ cell
 - (1) Defect questionable cause
 - (2) Injury by goitrogenic agents
 - Goiter
 - (1) Predisposition factors
 - (2) Unknown goitrogenic agents
- 2 Endemic goiter (see 15)

B POSTNATAL

- 1 Endemic or congenital goiter with failing secretory function
- 2 Iodine deficiency or administration (see Fig 157 Chart 35)
- 3 Antithyroid drugs
- 4 Irradiation
- 5 Thyroidectomy
- 6 Thyroiditis
- 7 Thyroid atrophy due to pituitary deficiency

X PATHOLOGY

A GROSS

- 1 Thyroid
 - a Complete absence, except for a few follicles^{15 18 1 43 45}
 - b Colloid adenoma with hyperplasia
 - c Colloid fetal embryonal adenoma
 - d Nodular goiter
 - e Simple goiter
 - f Diffuse hyperplasia
 - g Mixed
- 2 Pituitary
 - a Normal
 - b Hypertrophy¹⁸—weight from 0.7 to 2.42 Gm (average normal 0.6 Gm)
 - c Atrophy (rare)^{16 25}
- 3 Adrenals—normal
- 4 Gonads—small
- 5 Pancreas—normal
- 6 Thymus
 - a Normal
 - b Aplasia
- 7 Brain
 - a Size
 - (1) Normal
 - (2) Decreased somewhat
 - b Chronic meningitic alterations
 - c Hydrocephalus (slight)

B MICROSCOPIC

- 1 Without goiter (see 24 \ A 1)
 - a Complete fibrosis in some
 - b Parenchyma—variable amount, but always decreased
 - Lymphocytic infiltration common
- 2 With goiter—many variations from hyperplasia to cirrhosis (see 24 \ A 1 Figs 158 and 159)⁴⁰
- 3 Pituitary—see 2 IX II 14
- 4 Bones
 - a Dense
 - b Marrow very rich in fat
- 5 Muscles—hyaline degeneration

XI PATHOLOGIC PHYSIOLOGY

A SUMMARY

- 1 Essentially similar to adult myxedema with certain exceptions (see 24 XI)
- 2 Anterior hypophysis increases in size with thyroid failure
- 3 Pituitary eosinophilic cells
 - a Decrease
 - b Disappear
- 4 Growth hormone secreted by eosinophilic cells, decreases and is probably the chief cause of growth retardation
- 5 Injection of growth hormone stimulates growth in animals that are
 - Hypophysectomized
 - b Thyroidectomized
- 6 Long standing thyroid deficiency may ultimately decrease all pituitary function from lack of thyroid hormone by affecting the pituitary cells directly (cretins with thyroid atrophy)
- 7 Administration of desiccated thyroid may cause resumption of growth and nitrogen retention by reestablishing eosinophils to secrete growth hormone
- 8 Failure of growth with desiccated thyroid administration may indicate a nonresponsive pituitary (see 6 above)
- 9 Pituitary thyrotropic hormone
 - a Increases with decreased thyroid function
 - b Stimulates thyroid function possibly in cretins with goiter in whom responsive thyroid tissue is present

XII SYMPTOMATOLOGY

A GENERAL

- 1 Retardation of
 - a Growth
 - b Mental faculties
 - c Sexual development
- 2 Goiter may be present
- 3 Skin
 - a Dry
 - b Scaly
 - c Coarse
 - d Yellowish tinge in some
 - e Pale

B NEUROMUSCULAR AND SENSORY

- 1 Deafness
- 2 Mutism
- 3 Sleepiness
- 4 Lethargy
- 5 Fatigue
- 6 Weakness
- 7 Muscular hypotonia
- 8 Cold sensitivity
- 9 Tremors, late in disease if central nervous system affected
- 10 Tetany (India)¹⁰

C GASTRO INTESTINAL

- 1 Infant may have difficulty in nursing or taking feedings as well as swallowing due to
 - a Tongue enlargement
 - b Substernal goiter
 - c Pressure on the larynx from the goiter
- 2 Constipation
- 3 Anorexia
- 4 Weight gain uncommon

XIII DIAGNOSIS

A INTRODUCTION

- 1 Clinical differentiation of thyroid deficiency as listed at the beginning of the chapter depends on age of onset
 - a At or before birth
 - (1) Congenital athyreosis or thyroplasia
 - (a) Endemic
 - (b) Sporadic
 - (2) Cretinism with goiter
 - (a) Endemic
 - (b) Congenital or sporadic
 - b After birth—1 to 15 years
 - (1) Infantile myxedema

- (a) With goiter
- (b) Without goiter
- (2) Childhood myxedema
 - (a) With goiter
 - (b) Without goiter

II UNTREATED CRETIN (see 24 \II)

- 1 Mentally sluggish rare exceptions
- 2 Height age—decreased, depending on same factors as bone age (see 1 V A)
- 3 Bone age—retarded if disease is of sufficient duration
- 4 Sexual development—delayed
- 5 Cholesterol (plasma)—elevated usually
- 6 Iodine (serum organic)—decreased
- 7 Basal metabolic rate—low when obtainable⁷
- 8 Sella turcica—enlarged
- 9 Therapy produces striking response

C TREATED CRETIN (see Table 15)

- 1 Previous or concurrent treatment may make the diagnosis difficult because
 - a Mental retardation—may be slight
 - b Growth resumption takes place at a normal or accelerated rate
 - c Height age—corrected to a certain degree
 - d Bone age—lag may have been overcome
 - e Sexual development—may have occurred
 - f Normal values for
 - (1) Cholesterol (plasma)
 - (2) Iodine
 - (3) Basal metabolic rate
- 2 Prior inactive growth period should be proved
- 3 Sella measurement is helpful when enlarged (see 2 \IV G)
- 4 If the total evidence is
 - a Impressive continue with desiccated thyroid
 - b Inadequate
 - (1) Omit desiccated thyroid for 1 to 2 months
 - (2) Observe patient for development of
 - (a) Mental sluggishness
 - (b) Growth arrest
 - (c) Dry skin
 - (d) Cholesterol (plasma)—increase
 - (e) Basal metabolic rate—decrease

TABLE 15 THYROID DEFICIENT CHILD

UNTREATED		TREATED WITH THYROID (DESICCATED) OR SPONTANEOUS RETURN OF THYROID FUNCTION
Height age	Retarded	Less retarded
Bone age	Greater delay than height age	Chronologic age reached if treated before age of 10
Mental age	Subnormal in majority	Some improvement but remain below average
Mental activity	Sluggish (and hypokinesia)	Normal
Cholesterol (plasma)	High	Normal
Dental age by roentgenograms	Normal deciduous teeth remain	Normal deciduous teeth expelled
Sella turcica	Enlarged	Size increases with skeletal growth

D CRETINISM WITH EUTHYROIDISM (see Table 15 Figs 151 and 160)

- 1 Past history of thyroid deficiency
- 2 Goiter—always present
- 3 Height age—subnormal
- 4 Bone age—may approximate height age
- 5 Sexual development—normal

E CRETINISM WITH HYPERTHYROIDISM (see Table 15, Figs 150 and 161)

- 1 Hyperthyroid signs and symptoms
- 2 Goiter—always present
- 3 Height age—subnormal
- 4 Bone age—may approach chronologic age
- 5 Sexual development—normal

XIV DIFFERENTIAL DIAGNOSIS

A DWARFISM—see 91 IV, 92 95

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A SUMMARY

- 1 Mental disorders
- 2 Final height—see 24 XIII
- 3 Reproductive system
 - a Sexual development—delayed
 - b Sterility in majority, but may become pregnant⁷⁰
- 4 Deafness
- 5 Mutism
- 6 Tremor
- 7 Spasticity
- 8 Tetany (India)⁴⁶
- 9 Cardiac decompensation⁴⁴
- 10 Constipation (may be severe)
- 11 Infections—very common
- 12 Hyperthyroidism³

13 Discrete fetal adenoma may develop into malignant degeneration

14 Anemia (secondary)

15 Albuminuria

XVI TREATMENT (see Chart 39)

A MEDICAL

1 Desiccated thyroid (U S P)

a Comment

- (1) Medication can be given with very little danger in the young
- (2) Dose may be reduced if child becomes restless or irritable

b Dosage

- (1) First 6 months
- (2) Up to 3 years
- (3) Three to 9 years
- (4) Nine to 18 years

MG
GR DAILY
1/16 1/3
1/4 1/2
1
1 1/2

c Results⁷¹

(1) Mental state

- (a) Responsiveness improves
- (b) Mental age advances
- (c) Normal intelligence in few
- (d) Aptitude is generally low
- (e) Idiocy occasionally

(2) Growth rate (see Charts 36 37 and 39)

- (a) Initially—increases
- (b) Later — follows normal trend for height age

(3) Final height

- (a) Predestined height minus approximately that lost while thyroid deficient
- (b) Growth rate cannot be forced by overtreatment because of epiphyseal closure

- (4) Bone age
 - (a) Increases rapidly
 - (b) Progresses disproportionately to increase in height age
 - (c) May become normal for chronologic age
- (5) Goiter, if present, may decrease in size^{34, 35}
- (6) Hair
 - (a) Growth may be stimulated
 - (b) Hypertrichosis may disappear
- (7) Sexual development
 - (a) Breasts enlarge
 - (b) Menarche may be initiated
 - (c) Reproductivity probably normal
- (8) Urine
 - (a) Creatinine—increases^{36, 37}—40 to 50 mg
 - (b) 17 ketosteroids—may remain low³⁸
 - (c) Blood chemical analyses approach normal range for
 - (a) Cholesterol (plasma)
 - (b) Iodine (organic)
- 2 Methyltestosterone (see Chart 38)
 - a Indication—if no response with desiccated thyroid
 - b Dosage—oral, 10 to 20 mg daily
 - c Results
 - (1) Growth may be stimulated
 - (2) Basal metabolic rate may increase
- 3 Thyrotropic hormone
 - a Effective if responsive thyroid tissue is present
 - b Not available for clinical use
- 4 Growth hormone
 - a Indicated in cases who fail to grow with desiccated thyroid
 - b Not available for clinical use

B SURGICAL—Indications

- 1 Goiter, if
 - a Unusually
 - b Tracheal compression is found
- 2 Evidence suggesting malignancy

C COMPLICATIONS

- 1 Anemia
 - a Thyroid medication usually restores blood count to normal
 - b Iron may facilitate response
- 2 Hyperthyroidism (see 15, 24 & 1 A)

XVII PROGNOSIS

A WITHOUT TREATMENT (see Figs 164-167)

- 1 Absence of goiter
 - a Permanent state
 - b Mentality remains low
 - c Dwarfism
- 2 Presence of goiter
 - a As above
 - b Lesser degrees of mental and physical retardation
 - c Spontaneous recovery of normal or excess thyroid function with corresponding improvement depending on
 - (1) Duration before recovery
 - (2) Degree of deficiency

B WITH TREATMENT (see Figs 145-152, 162 and 163)

- 1 Factors
 - a Degree of deficiency
 - b Therapy depending on
 - (1) Time instituted
 - (2) Responsiveness
 - (3) Adequacy
- 2 Results—see 24 & VI A 1 c
- 3 Life expectancy normal¹

XVIII CAUSES OF DEATH

A UNTREATED

- 1 Premature aging
- 2 Intercurrent infection

B TREATED—No data

REFERENCES

- 1 Albright F. Changes simulating Legg-Perthes disease (osteochondritis deformans juvenilis) due to juvenile myxedema: report of case. *J Bone & Joint Surg* 20:764-769 (July) 1938
- 2 Baratz J J and Bronstein I P. Heart in children with thyroid deficiency. *Am J Dis Child* 64:415-474 (Sept.) 1954
- 3 Bartels E C. Hyperthyroidism developing in cretin. *S Clin North America* 25:672-678 (June) 1945
- 4 Benda C F and Bixby E N. Urinary excretion of 17 ketosteroids in various conditions of oligophrenia correlated with some autopsy observations. *J Clin Endocrinol* 7:503-518 (July) 1947
- 5 Bjarnason B and Miller P R. Hypothyroidism as cause of disease of hip. *Am J Dis Child* 55:1189-1211 (June) 1958
- 6 Beumer H and Fiske C. Der Kreatin Kreatinstoffwechsel bei Myxödem und Gesunden.

- unter Einwirkung von Thyreoidin Berlin Klin Wchnschr 57 1:8 181 (Feb.) 1920
- 7 Breitbarth H Studie über den Phosphorstoffwechsel bei der angeborenen Athyreose Ztschr f Kind rh 62 52 64 1940
 - 8 Bronstein I P Studies in cretinism and hypothyroidism in childhood blood cholesterol JAMA 100 1661 1663 (May) 1933
 - 9 — Diagnosis and prognosis of thyroid deficiency in childhood Illinois M J 84 206 210 (Sept.) 1943
 - 10 Bronstein I P Bower I F and Murphy J Familial cretinism 2 brothers exhibiting thyroid deficiency and epiphyseal dysgenesis Am J M Sc 205 114 117 (Jan.) 1943
 - 11 Brown A W Bronstein I P and Krames H Hypothyroidism and cretinism in childhood influence of thyroid therapy on mental growth Am J Dis Child 57 517 523 (Mar.) 1939
 - 12 Bruch H and McCune D J Mental development of congenitally hypothyroid children its relationship to physical development and adequacy of treatment Am J Dis Child 67 205 224 (Mar.) 1944
 - 13 Cavanaugh L A Shelton E K and Sutherland R Metabolic studies in osteochondritis of capital femoral epiphysis J Bone & Joint Surg 18 957 968 (Oct.) 1936
 - 14 Crawford T Carbohydrate tolerance in hypothyroidism and hyperthyroidism Arch Dis Childhood 15 184 198 (Sept.) 1940
 - 15 Curling T B Two cases of absence of the thyroid body and symmetrical swellings of fat tissue at the sides of the neck connected with defective cerebral development Med Chir Trans London 33 303 306 1850
 - 16 de Coulon W Ueber thyrotoidea und Hypophysen der cretinen sowie uher thyreoidale reste bei struma nodosa Arch f path Anat 147 53 99 1897
 - 17 Decourt J Le rôle du corps thyroïde dans la régulation de la chloremie Ann de méd 44 133 144 (July) 1938
 - 18 de Quervain F and Wegelin C Der endemische Kretinismus Berlin Springer 1936 p 101
 - 19 Dye J A and Mauhan C H Further studies of thyroid gland thyroid gland as growth promoting and form determining factor in development of animal body Am J Anat 44 331 379 (Nov.) 1929
 - 20 Engel M H Bronstein I P Brodie A G and Wesoke P Roentgenographic cephalometric appraisal of untreated and treated hypothyroidism Am J Dis Child 61 1193 1214 (June) 1941
 - 21 Erdheim J Ueber Schilddrüsenaplasie Beitr z path Anat u z allg Path 35 366 386 1904
 - 22 Fairbank H A General diseases of skeleton Brit J Surg 15 120 142 (July) 1927
 - 23 Falta Wilhelm The Ductless Glandular Diseases Philadelphia Blakiston 1916 pp 173 133 159
 - 24 Ibid pp 161 167
 - 25 Fan C Creatine and creatinine metabolism in hypothyroidism with special reference to lumbar tons of using creatinine in urine as standard of basal energy metabolism J Pediat 18 57 60 (Jan.) 1941
 - 26 Flesch M Ueber den Blutzuckergehalt bei Morbus Basedow und uher thyreogene Hyperglykämie Beitr Klin Chir 82 236-75 1913
 - 27 Gray H Blood sugar standards in cordials in either normal nor diabetic Arch Int Med 31 259 267 (Feb.) 1923
 - 28 Greene A M Iodine and cholesterol metabolism in patients with primary myxedema clinical and experimental study with report of results of treatment Arch Int Med 67 114 128 (Jan.) 1941
 - 29 Hees J H Blood cholesterol and creatine excretion in urine is aid to diagnosis and treatment of hypothyroidism Ann Int Med 8 604 611 (Nov.) 1934
 - 30 Hill A M and Webber J E Serum phosphatase values in children showing retardation in ocular development and low metabolic rates J Pediat 22 325 331 (Mar.) 1943
 - 31 Hummich H E Daly C Fazla J F and Herrlich H C Effect of thyroid medication on brain metabolism of cretins Am J Psychiat 60 489-493 (Jan.) 1942
 - 32 Howell L P The excretion of gonadotropic principle in thyroid disease Tr Am A Soc Gynec 1940 pp 157 159
 - 33 Hursthal L M Unpublished data
 - 34 Hursthal L M and Mulsin N Cretinism Am J Med 1 56 87 (July) 1946
 - 35 Janney N W III Studies in thyroid therapy Arch Int Med 22 187 217 (Aug.) 1913
 - 36 Johnston J A and Maroney J W Factors affecting retention of nitrogen and calcium in period of growth effect of thyroid on nitrogen retention Am J Dis Child 58 955 958 (Nov.) 1939
 - 37 Kendle F W Case of precocious puberty in a female cretin Brit M J 1 246 1905
 - 38 Langmann A G and Bruch H Carcinoma of the thyroid gland in children report of case associated with multiple anomalies of development with studies of basal metabolism serum cholesterol and creatinine excretion after thyroidectomy Am J Dis Child 56 616 633 (Sept.) 1933
 - 39 Lawen A Zur Kenntnis der Wachstumsstörungen am Kretinenskelett Deutsche Ztschr f Chir 101 454-466 1909
 - 40 Lerman J Jones H W and Callan E Studies on two sporadic cretinous brothers with goiter together with some remarks on the relation of hyperplasia to neoplasia Ann Int Med 25 677 701 (Oct.) 1946
 - 41 Lewis L A and McCullagh E P Electrophoretic analysis of plasma proteins in hyperthyroidism and hypothyroidism Am J M Sc 208 727 735 (Dec.) 1944
 - 42 Looser H Ueber die Ossifikationsstörungen bei Kretinismus Verhandl d deutsch path Gesellsch 24 352 360 1929
 - 43 MacCallum W G and Fabian M On the anatomy of a myxoedematous idiot Bull Johns Hopkins Hosp 18 341 345 1907
 - 44 Man E B Culotta C S Siegfried D A and Stilson C Serum precipitable iodines in recognition of cretinism and in control of thyroid medication J Pediat 31 154 160 (Aug.) 1947
 - 45 Maresch R Congenital Defect der Schilddrüse bei einem 11 jährigen Mädchen mit vorhandenen Epithelkörperchen Ztschr f Heilk 19 249 2 0 1898
 - 46 McCarrison R The Thyroid Gland in Health

and Dinea = New York Wood 1918 pp 141 147

47 McCrudden F H The effect of fat and of carbohydrate diets on the excretion of creatin in cases of retarded development J Exper Med 15 45 465 1912

48 Pineles F Ueber Thyreoplasie (Longenitales Myxoedem) und infantiles Myxoedem Wien klin Wchnschr 15 1129 1136 (Oct) 1902

49 Poncher H G Bronstein I P Wade H W and Ricewasser J C Creatine metabolism in hypothyroid infants and children further observations Am J Dis Child 58 20 296 (Feb) 1942

50 Poncher H G Valscher M H and Woodward H Creatine metabolism in children with hypothyroidism JAMA 103 1132 1135 (Apr) 1934

51 Radwin L S Michelson J P Melnick J and Gottfried M Blood lipid partition in hypothyroidism of children Am J Dis Child 60 1120 1136 (Nov) 1940

52 Reilly W A and Smyth F B Cretinoid epiphyseal dysgenesis J Pediat 11 786 796 (Dec) 1937

53 Ross D A and Schwab R S The cortical alpha rhythm in thyroid disease Endocrinology 25 75 79 (July) 1939

54 Scholz W Ueber den Stoffwechsel der Cretinen Zeitschr f exper Path u Therapie 2 271 384 (Oct) 1905

55 Schonemann A Hypophysis und Thyreoiden Virchow's Arch f path Anat 129 310 336 1892

56 Sharpey Schafer E P Recent advances in treatment endocrinology Practitioner 153 30 308 (Nov) 1944

57 Shelton H K and Tager B N Creatinuria and creatine tolerance in childhood with special reference to bone age and hypothyroidism Endocrinology 21 773 78 (Nov) 1937

58 Shorr E Richardson H B and Mansfield J Influence of thyroid administration on creatin metabolism in myxedema of adults Proc Soc Exper Biol & Med 32 1340 1342 (May) 1935

59 Smallpeice V Cretinism with goitre in infancy Lancet 1 565 568 (Apr) 1949

60 Smith J Plasma phosphatase in rickets and other disorders of growth Arch Dis Child hood 8 215 220 (June) 1933

61 Svendsgaard E Blood sugar in normal and sick children with special reference to coeliac disease Acta paediat (suppl 4) 12 1 249 1931

62 Talbot N B Influence of thyroid hormone on serum phosphatase Endocrinology 24 872 873 (June) 1939

63 Talbot N B Butler A M Berman R A Rodriguez M and MacLachlan E A Excretion of 17 ketosteroids by normal and by abnormal children Am J Dis Child 65 364 375 (Mar) 1943

64 Talbot N B Butler A M MacLachlan E A and Jones R N Definition and elimination of certain errors in hydrolysis extraction and spectrochemical assay of α and β neutral urinary 17 ketosteroids J Biol Chem 136 365 377 (Nov) 1940

65 Talbot N B Butler A M and Saltzman A H A congenital defect of water metabolism Am J Dis Child 59 325 326 (Sept) 1945

66 Talbot N B Hoeffel G Schwachman H and Tuohy E L Serum phosphatase as aid in diagnosis of cretinism and juvenile hypothyroidism Am J Dis Child 62 273 278 (Aug) 1941

67 Talbot F H and Moriarty M E Value of basal metabolism in diagnosis and treatment of cretinism Am J Dis Child 25 185 197 (Mar) 1923

68 Taylor G L and Appleton J L Jr Dental aspects of case of dwarfism (cretinism?) Dental Cosmos 71 124 131 (Feb) 1929

69 Topper A and Cohen P Effect of thyroid therapy on children Am J Dis Child 35 205 220 (Feb) 1928

70 Townsend C W A pregnant cretin Arch Pediat 14 20 1897

71 Turner J G Teeth of microcephalics and cretins Tr Odont Soc Gt Britain 34 1-4 (Oct) 1901

72 von Seemen A Osteochondropathia cretinoidea (Osteoarthrosis hypothyreotica) Arch f klin Chir 152 616 630 1928

73 Wagner R Endocrine problems in childhood Bull New England M Center 7 238 244 (Oct) 1945

74 Wilkins L Pates of growth osseous development and mental development in cretins and in dwarfs Am J Dis Child 54 193 194 (Apr) 1937

75 — Rates of growth osseous development and mental development in cretins as guide to thyroid treatment J Pediat 12 429 438 (Apr) 1938

76 Thyroid medication during childhood JAMA 114 2287 2387 (June) 1940

77 — Epiphyseal dysgenesis associated with hypothyroidism Am J Dis Child 61 13 34 (Jan) 1941

78 Wilkins L Fleischmann W and Block W Hypothyroidism in childhood sensitivity to thyroid medication as measured by serum cholesterol and creatine excretion J Clin Endocrinol 1 14 23 (Jan) 1941

79 Wilkins L and Fleischmann W Studies on creatinuria due to methylated steroids J Clin Investigation 24 21 37 (Jan) 1945

80 Woolley H V Jr and McCammon R W Bone growth in congenital myxedema use of serial roentgenograms of os radius in diagnosis and regulation of therapy during infancy J Pediat 27 229 235 (Sept) 1945

81 Zondek H The Diseases of the Endocrine Glands 4th (2nd English) Ed Baltimore Williams & Wilkins 1944 pp 203 226



FIG 145 CRETINISM (*Left*) Cretin with recurrent thyroid deficiency at 21 months having begun at 4 months of age and necessitating gastrostomy because of dysphagia thyroid palpable Note nodular goiter in mother (*Right*) Same patient at 12 years Irregular treatment prior to admission (Burroughs Well come thyroid $\frac{1}{4}$ gr daily = equivalent in 1/10 gr USP) Treatment thereafter was adequate in dosage but taken irregularly Idiocy Sella size 63 sq mm (Hurxthal L M and Musulin N Cretinism Am J Med 1 72 82)

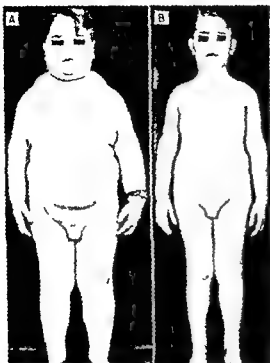


FIG 146 CRETIN (Left) Age 14 Substernal goiter (congenital) and concurrent thyroid deficiency before treatment Plasma cholesterol 360 mg % BMR minus 36% (Right) After 14 months treatment. (Hurxthal L M and Musuhn N Cretinism Am J Med 1 66 87)

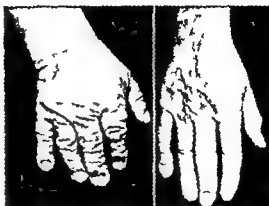


FIG 147 CRETINISM (Left) Hand of adult cretin (Right) Normal hand for comparison (de Quervain F and Wegelin C Der endemische Kretinismus Berlin Springer p 57)



FIG 148 CHILDHOOD MYXEDEMA WITH EXCESS HAIR GROWTH—RESPONSE TO DESICCATED THYROID

Chief complaints Retarded growth and mentally slow for 2 years

History of present illness No other complaints Menarche at 12 but irregular and scanty periods

Physical examination Age 13 years 9 months Weight 109 lbs Height 57 in Span 49¼ in

Height age 12 years Movements slow Edema of face Excess hair on neck side of face back and legs Marked hyperkeratosis of knuckles elbows and knees

Laboratory data Plasma cholesterol 225 mg % Serum phosphorus 3.1 mg % 17 keto steroids 6.3 mg /24 hrs

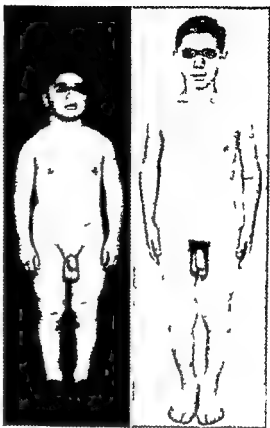
Roentgenographic findings Bone age 13 years 9 months

Treatment Desiccated thyroid 1½ gr daily for 3 months Plasma cholesterol 156 mg % Serum phosphorus 3.6 mg %

Progress Periods regular 5 days Skin smooth Loss of excess hair Weight 99 lbs Height 51¼ in

Comment This is one of several cases in which marked hirsutism accompanied myxedema and disappeared with treatment The normal bone age and the relatively slight increase in plasma cholesterol are interesting The loss in weight has masked the growth increase the latter being only ¼ in in 3 months (*Left*) Before therapy (*Right*) Three months later

FIG 149 CRETINISM—CONGENITAL ATHYREOSIS
Family history Negative
History of present illness Normal at birth At 6 months of age developed constipation which required hospital care Cretinism was recognized and desiccated thyroid was prescribed but in irregular and inadequate dosage At 15 years of age the child was only in the fifth grade
Physical examination Age 15 Weight 93 lbs Height 50½ in BP 96/60 Pulse 72 Sluggish mentally Tongue large thick Marked hair growth on back and legs Skin dry waxy pallor Thyroid not palpable
Laboratory data RBC 4 000 000 Hgb 72% Total protein 13 Gm % Plasma cholesterol 263 mg %
Roenigkographic findings Bone age 8 years 3 months Sella turcica 121 sq mm (enlarged) Numerous unerupted permanent teeth Twelve year molars unerupted
Treatment Desiccated thyroid 1 gr daily orally
Progress Growth of 4½ in in 11 months Weight 84 lbs Pubic and axillary hair developed but marked loss of body hair Total protein 67 Gm % Plasma cholesterol 158 mg % Bone age 10 years 9 months
(Top left) Before treatment
(Top right) One year later
(Bottom left) Photograph of hair on back before treatment
(Bottom right) Picture shows persistence of hair loss after a year



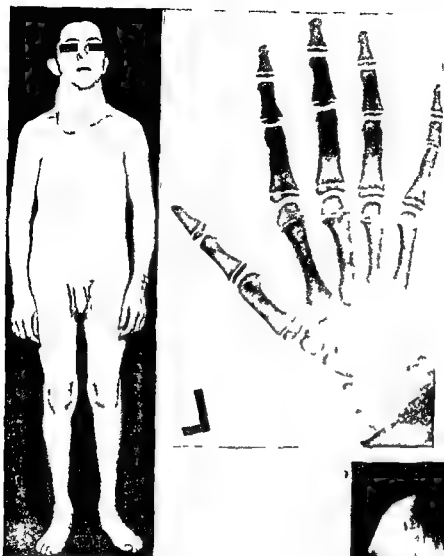


FIG 150 CONGENITAL GOITER Congenital goiter with antecedent thyroid deficiency and concurrent hyperthyroidism. At age 18 height age 12 years bone age 13 years. Increase in size of goiter beginning at age 16 with spurt in growth. Greater activity of thyroid in the past 2 years caused the bone age 13 to approximate the height age 12 (Hurxthal L M and Musulin M. Cretinism Am J Med 1 66 82)

FIG 151 CRETINISM Age 38 Goiter since birth. Intra-thoracic goiter with pressure on trachea. Entered school at 9 finished at 24. Weight 88 lbs Height 56 in BMR plus 6%. Goiter was removed. Pathologic report: multiple colloid adenomatous goiter with secondary hyperplasia. Example of cretinism with subsequent normal function. Postoperative plasma cholesterol 324 mg %. Clinical thyroid deficiency corrected with desiccated thyroid. Bella measured 74 sq mm which is above average for height age of 12.



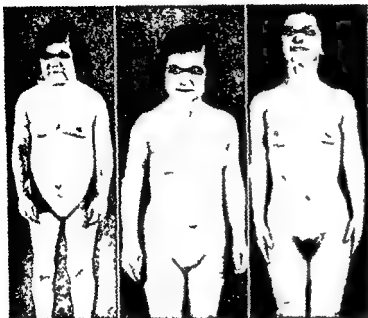


FIG 152 CRETIN Age 17 Irregularly and inadequately treated. Onset in infancy, no palpable thyroid, presumably congenital athyreosis. (Left) Before institution of adequate therapy. Plasma cholesterol 430 mg % BMR minus 18%. Lone age 11½ years. (Center) After 3 months of treatment. 10 g of desiccated thyroid per week. (Right) After 1 year of treatment. Height 49½ in at 18 2 years later 53½ in. Pregnancy occurred later with normal baby. For bone changes see Figure 153 (Huruthal L M and Musulin N Cretinism Am J Med 16: 87)

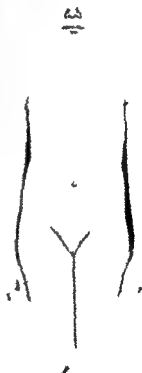


FIG 153 CRETIN (See also Fig 154 Chart 37) Cretin with concurrent thyroid deficiency and a palpable thyroid gland of colloid type before treatment. Age 11 years. Height age ½ years. Bone age 7¼ years. Plasma cholesterol 316 mg % BMR minus 32%. There was no apparent retardation in mental age; the child was mentally alert. (Huruthal L M and Musulin N Cretinism Am J Med 16: 87)



FIG 154 CRETIN (See also Fig 153) Skull of a cretin showing an enlarged sella. Sella measures 11 mm deep and 11 mm anteroposteriorly. Average normal measurements for this age (11 years) are 9.36 by 6.18 mm (Hurtthal L M and Musuhn N Cretinism Am J Med 1 78 82)

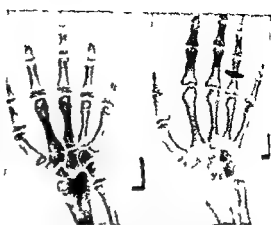


FIG 155 ROENTGENOGRAM OF A CRETIN'S HAND (See also Fig 152) (Left) Age 17 female with concurrent thyroid deficiency in which previous treatment was inadequate (Right) After 3 years of treatment complete epiphyseal closure. Note dense and widened phalangeal bones due to longstanding hypothyroidism. Height age at 18 years was 8 years at 20 10 years. Puberty began during the first year of treatment (Hurtthal L M and Musuhn N Cretinism Am J Med 1 67 82)



FIG 156 CRETINISM Juvenile osteochondritis deformans in cretinism (de Quervain F and Wegelin C Der endemische Kretinismus Berlin Springer p 47)

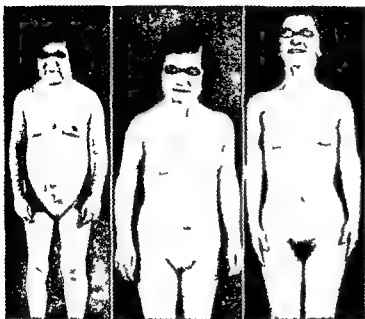


FIG 152 CRETIN Age 17 Irregularly and inadequately treated. Onset in infancy; no palpable thyroid presumably congenital athyreo is (Left) Before institution of adequate therapy Plasma cholesterol 430 mg % BMR minus 18% Bone age 11 $\frac{1}{4}$ years (Center) After 3 months of treatment 10 gr of desiccated thyroid per week (Right) After 1 year of treatment Height 49 $\frac{1}{2}$ in at 10 2 years later 53 $\frac{1}{2}$ in Pregnancy occurred later with normal baby For bone changes see Figure 155 (Hurthall L M and Musulin N Cretinism Am J Med 1 66 32)

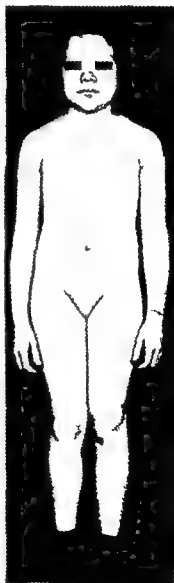


FIG 153 CRETIN (See also Fig 154 Chart 3.) Cretin with concurrent thyroid deficiency and a palpable thyroid gland of colloid type before treatment Age 11 years Height age 8 $\frac{1}{2}$ years Bone age 7 $\frac{1}{4}$ years Plasma cholesterol 316 mg % BMR minus 3% There was no apparent retardation in mental age the child was mentally alert (Hurthall L M and Musulin N Cretinism Am J Med 1 66 32)



FIG 154 CRETIN (See also Fig 153) Skull of a cretin showing an enlarged sella Sella measures 11 mm deep and 11 mm anteroposteriorly Average normal measurements for this age (11 years) are 9.36 by 6.18 mm (Hurxthal L M and Musulin N Cretinism Am J Med 1 78 82)

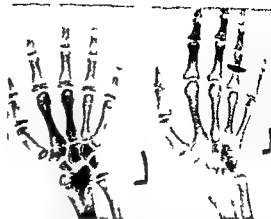


FIG 155 ROENTGENOGRAM OF A CRETIN'S HAND (See also Fig 152) (Left) Age 17 female with concurrent thyroid deficiency in which previous treatment was inadequate (Right) After 3 years of treatment complete epiphyseal closure Note dense and widened phalangeal bones due to long standing hypothyroidism Height age at 18 years was 8 years at 20 10 years Puberty began during the first year of treatment (Hurxthal L M and Musulin N Cretinism Am J Med 1 67 82)

FIG 156 CRETINISM Juvenile osteochondritis deformans in cretinism (de Quervain F and Wegelin C Der endemische Kretinismus Berlin Springer p 47)



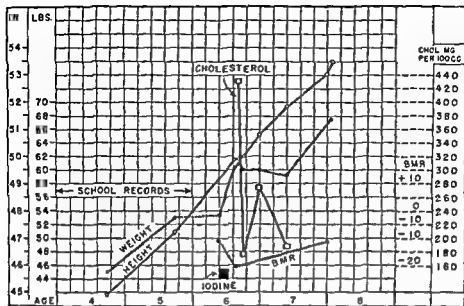


CHART 35 IODINE INDUCED MYXEDEMA (See also Fig 157) Effect of iodine administered to child of 6 with colloid goiter resulting in clinical myxedema with high plasma cholesterol and low BMR. The unusual effect suggests colloid goiter with some areas of hyperplasia or hyperplasia alone which became involuted when iodine was given. The weight and the height curves suggest a preexisting mild hyperthyroidism even though the BMR recorded was minus 11% (Hurxthal L M Myxedema and its various causes S Clin North America 25 65: 671)

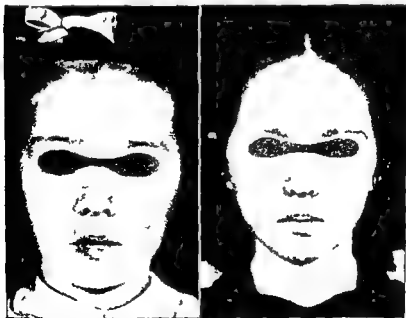


FIG 157 MYXEDEMA From administration of iodine in a girl of 6 with colloid goiter (See also Chart 35) (Left) After taking Lugol's solution 5 to 10 drops daily for months Weight 61 lbs Pulse 76 Plasma cholesterol 432 mg % BMR minus 21% (Right) After discontinuing iodine Weight 60 lbs Pulse 104 Plasma cholesterol 19 mg % Subsequent course normal Gland continued to be easily palpable and felt like a colloid gland Eight year follow up—patient normal in every way (Hurxthal L M Myxedema and its various causes S Clin North America 25 65: 671)



FIG 158 CRETINISM (See also Fig 159) Papilliferous hyperplasia associated with clinical myxedema in a child Possible effect of iodine (Klose H Die Chirurgie der Basedowschen Krankheit Stuttgart Enke II 319)



FIG 160 CONGENITAL GOITER Sister of patient shown in Figure 150 previous thyroid deficiency (cretinism) and current euthyroidism (normal thyroid function) Age 20 Height age 10 $\frac{3}{4}$ years Height 55 in Bone age normal Cata menia at 17 years of age Mental status retarded Plasma cholesterol 1.6 mg % BMR plus 12% Thyroid deficiency existed during childhood causing delayed puberty Function evidently revived around age of 12 to 15 years (Hurxthal L M Myxedema and its various causes S Clin North America 25 657 671)

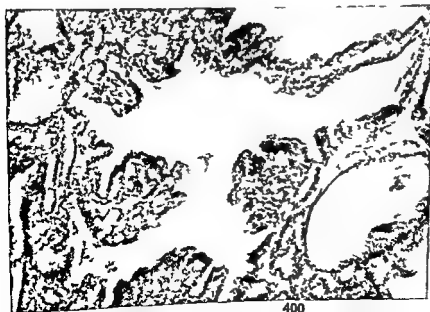


FIG 159 HISTOLOGY OF GOITER IN A CRETIN Papilliferous epithelium in large nodular or endemic type goiter removed from a cretinous child

FIG 161 CRETINISM WITH CONCURRENT EUTHYROIDISM AND SUBSEQUENT HYPERTHYROIDISM Age 11 male Height age 7 years Bone age 5 years Mentally alert no evidence of concurrent thyroid deficiency Plasma cholesterol 212 mg % BMR plus 12% The goiter had increased in size before admission and there had been an improvement in growth rate mental and physical activity The retarded height age and bone age are stigmata of previous thyroid deficiency After subtotal thyroidectomy desiccated thyroid was prescribed and taken for several years At age of 22 patient returned with recurrence of goiter and hyperthyroidism (BMR plus 32%) First pathologic report colloid adenomatous goiter Second report (at age 22) colloid adenomatous goiter with areas of hyperplasia (Bartels E C. Hyperthyroidism developing in a cretin S Clin North America 25 672 678)



FIG 162 CHILDHOOD MYXEDEMA (Left) Age 13 Duration 1 year Chief complaints languor and weight gain Weight 116 lbs Height age 12½ Bone age 12¾ years Sella meas 9 x 10 mm (average normal 9.6 by 6.8 mm) RBC 3 600 000 Hgb 10% Plasma cholesterol 416 mg % Blood sedimentation rate 60 mm/hr Thyroid uniformly enlarged firm suggesting thyroiditis Patient continued to do well in school despite her lethargy Dis likes cold weather Slight secondary sex development including pubic hair but not catamenia (Right) One year later Treatment 1 gr of desiccated thyroid daily Weight loss of 10 lbs with treatment then recovered to 109 lbs Grew 2¾ in in year (normal rate at this age 1½ in) Menstrual periods began after 3 months of treatment RBC 4 000 000 Hgb 90% Plasma cholesterol 176 mg % Two years later height 62½ in Thyroid normal in size with only slight firmness Patient grew a total of 4 in and changed from 40 to 60 percentile curve of Burgess Weight 116 lbs Plasma cholesterol 182 mg % Sedimentation rate 16 mm/hr Bone age 14 3 years This case illustrates slight lag in bone age because of short duration of thyroid deficiency and regression of enlarged thyroid (Hurxthal L M Cretinism M Clin North America 32 127 139)

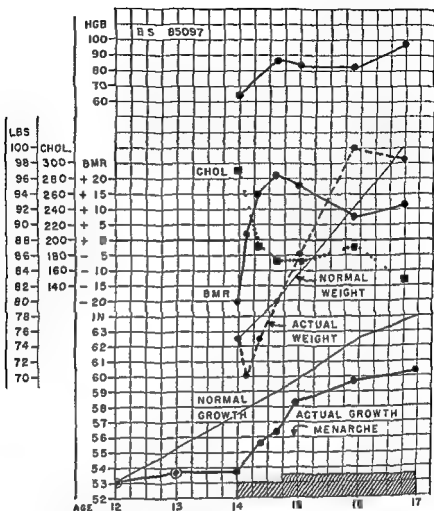


CHART 36 CHILDHOOD MYXEDEMA Age 14 Chart depicts the acceleration of growth on giving desiccated thyroid. The change in plasma cholesterol BMR and Hgb are shown. In spite of growth retardation and failure of secondary sex development and dry skin the patient's mental age or alertness apparently was not retarded. Patient was graduated from college and on thyroid has been normal ever since. On stopping thyroid on one occasion evidence of thyroid deficiency soon became apparent. Note initial drop in weight and then increase as anabolic effects (stimulation of growth hormone) followed. One shaded block equals 1 gr daily of desiccated thyroid (U S P). Dot in circle indicates height recorded at school.

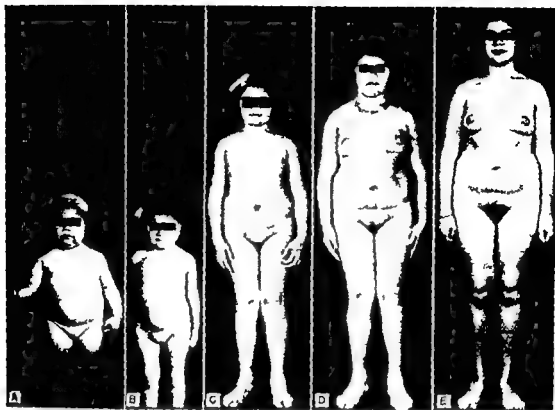


FIG 163 CRETINISM INFANTILE MYXEDEMA OR CONGENITAL ATHYREOSIS (A) Age 7 Unable to walk unaided Marked flat feet and lumbar lordosis Patient had received inadequate and irregular treatment previously Plasma cholesterol 460 mg % BMR minus 26% Bone age 9 months which strongly indicated congenital athyreosis Sella 9 x 13 mm Adequate treatment started (B) Three months later (C) Age 12 (D) Age 16 Patient had not taken thyroid for some time (E) Final result Age 18 Normal intelligence Height age retarded Radial epiphyses closed Sella 11 x 14 mm It is believed that the early (although inadequate) treatment in infancy was responsible for the normal intelligence attained (Hurxthal L M and Musulin N Cretinism *Am J Med.* 1 72 82)

CHART 37 GROWTH IN CHILDHOOD MYX EDEMA (See also Figs 153 154) Note spurt in growth on desiccated thyroid (1 gr a day) and compare with expected growth of normal aver age child of 11 (50% curve of Burgess) and a normal short child of 11 whose height is less than 9 years and falls upon the 4% curve Pa tient has gone from height age of 8 3/5 years at 11 to a height of 11 4/5 years at 13 (in 26 months) After the initial spurt in the first year or so growth rate levels off to normal

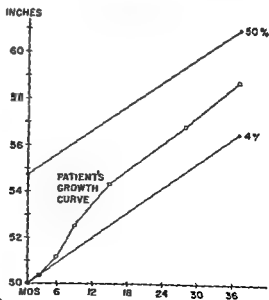


CHART 38 CRETINISM Chart shows nitrogen retention (shaded area) on giving thyroid (solid black) to a 4½ year old cretin in spite of weight loss due to extracellular fluid

Period A—actual weight then increased and continued to do so even when thyroid was discontinued and methyltestosterone was given

Period C—note loss of accumulated fluid due to androgen when thyroid given again and greater output of urinary nitrogen

Period K—which may not have represented tissue nitrogen but stored nitrogen Methyltestosterone is said to stimulate growth in cretins unresponsive to thyroid (Wilkins L Conference on Metabolic Aspects of Convalescence 9th meeting Feb 23, New York, Macy pp 160 167)

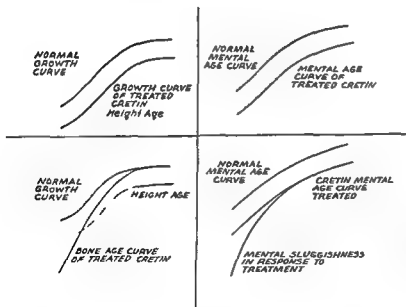
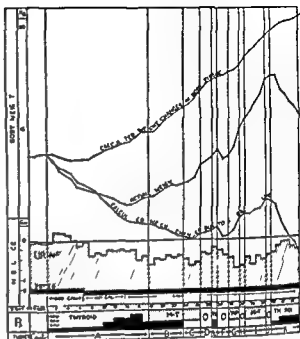


CHART 39 CRETINISM
Diagrammatic illustration of effect of treatment or resumption of normal thyroid function in cretins. The theoretical relationships between height age, bone age and mental activity are shown (Hurxthal L M and Musulin N Cretinism Am J Med 1 66 82)



FIGS 164 (Left) and 165 (Right) CRETINS WITHOUT GOITER (European) (de Quervain, F and Wegelin C Der endemische Kretinismus Berlin Springer, pp 37 and 78)



FIG 166 (Left) CRETIN WITH HANGING GOITER (European)
FIG 167 (Right) CRETIN FROM MOUNTAINOUS AREA WITH SMALL IN
TRITHORACIC GOITER (European)
(de Quervain F and Wegelin C Der endemische Kretinismus Berlin
Springer pp 32 and 33)

SECTION 25

MYXEDEMA

SYNONYMS

Gull disease

Primary thyroid deficiency or atrophy

Hypothyroidism

Athyreosis

I DEFINITION

Myxedema is a condition which results from hypofunction of the thyroid gland with marked underproduction of thyroid hormone. It is usually characterized by non pitting edema, especially about the eyes, dry skin, slow pulse, mental lethargy, and is further identified by a low basal metabolic rate, elevated plasma cholesterol and low blood iodine.

II APPEARANCE

Lethargic individual with puffiness about the eyes, bloated (see Fig 168)

III AGE

Any (see Cretinism), but only adult myxedema is described in this section, usually in fourth or fifth decade, average 51±

IV SEX

Females more often affected than males, ratio 4 : 1

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal variations

B RESPONSIVENESS

Poor, slow, seem hampered

C OTHER ABNORMALITIES

Memory impaired sluggishness, lethargy, little irritability, emotional response slow, whimsical, rarely psychosis with or without hallucinations or other mental aberrations²

VI PHYSICAL STATUS

A NUTRITION

Good

1 Weight

Variable, normal or below in 40 per cent (see Fig 169)^{1,3}

2 Fat distribution

Pyknic type, uniform distribution, but may show predilection for nape of neck and supraclavicular areas

B HEIGHT

Normal variation

C EXTREMITIES

Normal contours, unless overweight

1 Upper

a Hands

May be edematous and so appear fat pawlike, cold

b Fingers

Normal

c Span

Normal

2 Lower

a Feet

As hands

b Toes

As fingers

D SPINE

Normal

E INTEGUMENT

1 General

Thickening of subcutaneous tissue causing nonpitting edema may be localized

a Texture

Rough slight scaling wrinkling even with edema hyperkeratosis of feet (see Fig 170)

b Temperature	Subnormal, cool to touch
c Moisture	Dry very little sweating
d Eruptions	Psoriasis, atopic eczema xanthomatosis ⁷⁰
e Pigmentation	Patchy cafe au lait
f Color	Yellow, waxy pallor may have pink cheeks
g Nails	Brittle thick slow growth
2 Hair	
a Head	Dry brittle, often fine falls out easily, diffuse or spotty alopecia may be present, poor growth will not hold permanent wave (see Fig 171)
b Facial	Sparse beard eyebrows scant or normal, rarely increased (see Fig 172) ⁷¹
■ Axillary	Normal scant or absent (see 96 III B C)
d Pubic	Normal scant or absent
e Body	Normal rarely increased or may be decreased ⁷²
F HEAD	
1 Shape and size	Normal, may appear obese because of edema
2 Facial expression	Dull sleepy bloated
3 Eyes	
a General	Puffiness of lids, watery eyes narrow palpebral fissures pig-eyed sometimes
b Fundi	Normal or sclerotic vessels
c Visual	
(1) Fields	Normal
(2) Acuity	Normal occasionally may be diminished
4 Ears and nose	Deafness is common (nerve and/or middle ear) nose may be normal or slightly larger because of subcutaneous edema
5 Mouth and throat	
a General	Lips may appear puffy pale, tongue may be swollen pale or reddish may have glossitis (possible vitamin B deficiency and rarely pernicious anemia)
b Teeth	Normal or tendency to decay
■ Larynx (voice)	Hoarse, deep edema of cords
G NECK	
1 General	Normal or fat
2 Thyroid	Usually not palpable except in thyroiditis colloid or nodular goiter may be present hyperplasia may be due to drugs (see 14 IX B 1 d, e, f g 24 IX)
H CHEST	Normal shape and size supraclavicular fat pads pleural effusion occurs occasionally
I HEART AND PERIPHERAL VESSELS	
1 Heart	May be increased in transverse diameter (due to fluid and/or dilatation) apical beat feeble ^{27 48 55 58 75 82 94 95 104 114 118}
2 Rate and rhythm	Bradycardia often may be normal or even increased in nervous individuals
3 Blood pressure	May be normal low not infrequently elevated when low systolic pressure consider possibility of pituitary origin systolic pressure above 150 in 50 per cent of cases diastolic pressure above 90 in 40 per cent ^{111 113}
4 Peripheral arteries and veins	Normal or slow arteries may be sclerotic

5 Vasomotor	Subnormal response
J BREASTS	
1 Male	Normal
2 Female	Normal or atrophy
K ABDOMEN	
1 Liver	Normal
2 Spleen	Normal
3 Hernia	None
4 Tumor	None
5 Ascites	May occur ^{37 38 50 103 161}
L GENITALIA	
1 Male	
a Penis	Normal
b Testes	Normal
c Prostate	Normal
2 Female	
a External	Normal (see hair)
b Internal	Normal
M NEUROMUSCULAR	
1 Muscles	Normal or may be weak and flabby, hypotonic
2 Gait	Normal, slow, tendency to waddle, clumsy (also hand movements)
3 Tremor	None
4 Paresthesias	Normal or may be present in hands and feet
5 Reflexes	Normal or hypoactive
6 Vibration sense	Decreased, probably due to impaired perception
N SPEECH	Slow, dull, hesitant

VII LABORATORY DATA

A URINE	
1 General	Normal, may have oliguria
2 Special chemical analyses	
a Sugar	Absent
b Albumin	Small amounts may be found
c Nitrogen	Normal or decreased ^{13 38 14 17}
d Creatine	Normal or decreased ^{11 1 6 141 142 154 168}
e Creatinine	Normal or decreased ^{14 154 166}
f Sodium	Normal retention during onset ^{14 17}
g Potassium	Normal retention during onset ¹⁷
h Calcium	Decreased ^{3 4 1 8 133}
i Phosphorus	Decreased ^{3 4 133}
j Chlorides	Normal or decreased ¹⁴⁶
k Iodine	Decreased ⁹
B HEMATOLOGY	
1 Red blood cells	Normal or decreased more often (about 3 to 4 million) 16 37 66 71 8 89 97 106 116 117 119 124 159 primary anemia has been reported ^{13 53 100 115}
2 Hemoglobin	Normal or decreased (about 70%), rarely increased ^{3 40} 68 8 108
3 White blood cells	Normal or decreased ^{10 16 8 68 8 88 105}
4 Differential	Normal or may have increased basophils and eosinophils relative lymphocytosis ^{10 16 37 8 88 105}

5 Reticulocytes	Normal ⁴
6 Bone marrow	Hypoplasia in longstanding cases ⁵
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal or decreased
2 Nonprotein nitrogen	Normal rarely increased
3 Protein (plasma)	Normal or may be increased (up to 8 Gm %) ^{6 98 106} 140 1 1
a Albumin	Normal or decreased ^{99 140 148}
b Globulin	Normal or decreased ^{140 148}
c Gamma globulin	Decreased ⁹⁸
d Beta globulin	Increased ⁹⁸
e A/G ratio	Normal or decreased (average 1.21) ^{98 140 148}
f Fibrinogen	Normal ⁹⁹
4 Uric acid	Normal or decreased
5 Cholesterol	Increased in 95 per cent of cases ¹⁴⁸ usually 100 per cent or more elevated depending on the level before onset of myxedema (see Charts 40 41) ^{7 13 0 81 59 73 74 70 9 94}
6 Sodium	Normal
7 Potassium	Normal
8 Calcium	Normal ^{3 4 44 133}
9 Phosphorus	Normal or decreased ^{3 4 44 133}
10 Phosphatase	Normal or decreased ^{14 131}
11 Chlorides	Normal ^{0 110}
12 Iodine	Decreased (total and plasma bound) rarely ^{5 21 4 29 98} ^{78 101 107 121 1 8 113 137 138 1 3-100 167}
13 Creatine	Normal or decreased ^{1 6}
14 Creatinine	Normal
15 Free fat	High ^{60 61}
16 Lipid phosphorus	High, ^{61 60 61} there is no correlation between height of cholesterol and level of neutral fat in serum
17 Magnesium	Normal (serum) but ultrafiltrable fraction above nor- mal and nonfiltrable (bound) fraction is absent ²⁷
D FUNCTION TESTS	
1 Tolerance	
a Glucose	Variable may be increased (low curve) (see Table 102) ^{1 4 40 57 80 81 87 91 90 163}
b Glucose insulin	No data
c Insulin	Slow initial fall (insulin resistance) ¹⁷
d Galactose	
(1) Oral	Increased (flat curve) question of retarded absorption ⁵ ^{143 14}
(2) Intravenous	Normal ¹¹
e Iodine	More retained in blood stream than normal, average in- crease 39 per cent curve greater than normal and falls slowly to basal level ^{130 170 122 14 163}
f Creatine	Normal or increased (increases with treatment 1 = 87% average retention of amount ingested) ^{241 1 4 156}
2 Adrenal water	Usually negative (see 6) ⁹⁷
3 Salt deprivation	Normal ^{96 116}
4 Balance	
a Nitrogen	Positive, at least during onset ^{3 1 17 133}
b Calcium	Positive or negative
c Phosphorus	Positive ^{3 133}

5 Renal	
a Phenolsulfonphthalein	Normal ⁹³
b Urea clearance	May be diminished ⁹
c Concentration	Normal, unless nephritis is an associated disease ⁹
6 ACTH	Eosinophils show a subnormal response ¹²⁰
E MISCELLANEOUS	
1 Basal metabolism rate	Low, rarely may be normal (see Chart 40)
2 Circulation time	Prolonged (arm to tongue 15 to 25 sec), minute volume decreased ^{100 108 147}
3 Sedimentation rate	Normal
4 Specific dynamic action of protein	Decreased
5 Gastric analysis	Hypochlorhydria and achlorhydria (gastroscopy may reveal atrophy) ^{84 99}
6 Electrocardiogram	Usually some change, low QRS complexes, low or flat T waves, may return to previous normal state with therapy (see Figs 173 and 177)
7 Blood volume	Decreased or increased ¹⁵¹
8 Spinal fluid protein	Increased ^{1 133}
9 Fecal excretion ¹³¹	
a Calcium	Normal or decreased
b Phosphorus	Normal or decreased
10 Electroencephalogram	Alpha rhythm decreased, about 6/sec ¹³³
11 Capillary permeability	Increased (fluorescein method) ^{90 108 109}
12 Carotin	May be present ^{3 37 1 7}
F URINARY HORMONE ASSAYS	
1 FSH	Negative, occasionally positive, may be increased (25 r u and over, exclusive of menopausal group) ^{7 38 40 69 80}
2 LH	No data
3 Estrogens	Normal
4 Pregnanediol	No data
5 17 ketosteroids	Very low, about 2 to 4 mg/24 hrs, may not increase with therapy in spontaneous myxedema ^{33 35 40 49 85 107}
■ Androgens (capon test)	Very low ¹⁰⁶
6 11 oxysteroids	Very low ^{43 149}
7 Aschheim Zondek	Negative
8 TSH	Increased (in blood and urine) or absent (blood) ^{18 19 31 41 63 ■ 110 1 9 144}
G BIOPSY	
1 Endometrial	May show hyperestrinism (metropathia hemorrhagica)
2 Testicular	No data possibly retarded spermatogenesis
H VAGINAL SMEAR	Normal or hypoestrin effect
I SEMEN ANALYSIS	Normal or oligospermia ¹³⁴
VIII ROENTGENOGRAPHIC FINDINGS	
A SKULL	
1 Cranial vault	Normal
2 Sella turcica	Normal or may be enlarged from aneurysm (see 2 XIV H 9 Fig 180)
3 Mandible	Normal
4 Sinuses	Normal
5 Teeth	Normal or decayed

B EPIPHYSEAL STATUS (bone age)	Normal
C LONG BONES	Normal
D VERTEBRAE	Normal
E BONE TEXTURE	Increased calcification or density ³
F MISCELLANEOUS	
1 Chest	Majority of cases show some enlargement of cardiac shadow often due to fluid (see Fig 174)
2 Arteries	Often calcified

IX ETIOLOGY

A SPONTANEOUS MYXEDEMA

- 1 Cause not known
- 2 Atrophy of thyroid gland may be found

B THYROIDITIS

- 1 Types
 - a Nonspecific (see 20 \)
 - b Riedel (see 21 \I)
 - c Hashimoto (see 22 \I)
- 2 Cause unknown

C PITUITARY FACTOR (see 6)

- 1 Antecedent and relative thyroid hypofunction may develop before the onset of pituitary failure
- 2 Selective deficiency of pituitary thyroid tropic hormone may be postulated

D SURGICAL—Myxedema may follow

- 1 Subtotal thyroidectomy for
 - a Hyperthyroidism
 - b Thyroiditis
 - c Nodular goiter which is the result of previous thyroid deficiency (see 15 \II B 1)
- 2 Total ablation of thyroid

E IRRADIATION — Hypothyroidism develops after

- 1 Roentgen therapy (often temporary)
- 2 Radioactive iodine

F GOITROGENIC AGENTS

- 1 Thiouracil
- 2 Propylthiouracil
- 3 Potassium thiocyanate (occasionally)

G IODINE—Ingestion may rarely produce myxedema (see Fig 157)^{6 7 17}

X PATHOLOGY

A GROSS

- 1 Thyroid (see 14 IX A Table 11)
 - a Size
 - (1) Normal
 - (2) Enlarged
 - (3) Small (atrophic)
 - (4) Thin

b Consistency

- (1) Firm
- (2) Like muscle

c Fibrous tissue increased

d Cysts or nodules may be found

e Cut section

- (1) Pale
- (2) Homogenous

2 Pituitary—size

- a Normal
- b Enlarged sometimes

3 Heart and blood vessels

- a Cardiac muscle
 - (1) Pale
 - (2) Flabby
 - (3) Friable
 - (4) Pseudohypertrophy due to swelling of fibers

b Pericardium—serous effusion and/or transudate if congestive heart failure complicates picture

c Weight of heart may be increased due to edema or actual hypertrophy when associated with hypertension

d Aorta

- (1) Sclerosis increased
- (2) Cystic degeneration may occur³⁴
- (3) Spontaneous rupture rarely

e Other blood vessels (see Fig 176)

- (1) Arteriosclerosis frequent
- (2) Coronaries often involved

4 Liver¹¹

- a Edema
- b Sclerosis
- c Central necrosis

5 Spleen¹¹

- a Congested
- b Sclerotic

6 Bones—calcification increased

7 Muscles¹¹

- a Pale
- b Edematous

8 Serous cavities—fluid may accumulate in all in variable amounts³

- 9 Kidney
 - a Normal
 - b Interstitial nephritis
- 10 Brain
 - a Variable findings
 - b Subarachnoid or choroid plexuses may show¹¹¹
 - (1) Edema
 - (2) Degeneration
- B MICROSCOPIC
 - 1 Thyroid
 - Tissue may be absent
 - b Fibrosis abundant
 - c Lymphoid and plasma cell infiltration
 - d Follicles (see Fig 175)
 - (1) Absent almost entirely
 - (2) Few may be scattered
 - (3) Colloid found occasionally
 - (4) Lack an epithelial lining
 - (a) Partially
 - (b) Completely
 - e Hyperplasia
 - f Endemic goiter
 - Fetal adenoma
 - 2 Pituitary⁸
 - a Eosinophils decreased
 - Basophils increased
 - c Colloid material is excessive in the pars intermedia
 - 3 Skin^{11 131}
 - a Collagen and elastic fibers are widely separated
 - b Corium shows
 - (1) Edema
 - (2) Mucinouslike material
 - c Epidermis has
 - (1) Hyperkeratosis
 - (2) Irregular atrophy
 - d Layers have perivascular and lymphocytic infiltration
 - 4 Muscles¹¹¹
 - a Edema
 - b Fibrosis
 - c Lipochrome may be present
 - d Vacuolization
 - Poor striations
- 2 Hair
 - a Fine
 - b Coarse
 - c Brittle
 - d Scant, falls out easily
 - Permanent wave does not take very well
- 3 Drug sensitivity, especially to
 - a Sedatives
 - b Narcotics
- 4 Hoarseness
- II NEUROMUSCULAR AND SENSORY
 - 1 Cold sensitivity
 - 2 Memory poor
 - 3 Mental sluggishness
 - 4 Sleepiness
 - 5 Deafness
 - 6 Joint pains
 - 7 Muscle
 - a Stiffness
 - b Soreness
 - 8 Weakness
 - 9 Fatigue
 - 10 Vertigo (labyrinthine)
 - 11 Dizziness
 - 12 Convulsions¹¹³
- C CARDIOVASCULAR
 - 1 Angina of effort
 - 2 Dyspnea
 - 3 Edema
- D GASTRO INTESTINAL
 - 1 Bloating
 - 2 Distention
 - 3 Constipation
 - 4 Weight gain
 - 5 Anorexia
 - 6 Dysphagia
- I GENITO URINARY
 - 1 Menorrhagia
 - 2 Oligomenorrhea
 - 3 Amenorrhea
 - 4 Sterility
 - 5 Abortions
 - 6 Libido decreased
 - 7 Impotence

XI SYMPTOMATOLOGY

A GENERAL

- 1 Skin
 - a Dry
 - b Coarse
 - c Cool

XII PATHOLOGIC PHYSIOLOGY

A INTRODUCTION (see Chart 50, p 479)

- 1 Pathologic changes that take place in myxedema are due to a deficiency of thyroid hormone which apparently is a catalyst and affects the anabolic and the catabolic processes of all body cells

2 Degree of deficiency necessary to produce myxedema

- It is generally assumed that myxedema results from practically complete loss of thyroid function
- b Hypophysectomy does not produce typical myxedema indicating that the thyroid is capable of low degree of function independent of pituitary
- c Various degrees of clinical myxedema can be produced by increasing or decreasing the dose of desiccated thyroid given to an athyroidal person
- d The pathologic process which produces relative thyroid deficiency probably progresses in most instances to complete destruction of secreting tissue except in nodular goiter
- e Because of the above it may be assumed that thyroid deficiency usually means athyroidism except during the period of transition from normal to complete loss

B ALTERATIONS IN PHYSIOLOGIC CHEMISTRY

- 1 There is decreased excretion (urinary and fecal) of the following as a result of lowered metabolism due to deficient thyroid hormone
 - a Creatine
 - b Nitrogen
 - c Urea
 - d Calcium
 - e Phosphorus
 - f Iodine
- 2 Iodine function in the body is decreased for little or none is used in thyroid hormone synthesis but some must be retained in tissue fluids since there is a
 - a Reduction in¹³⁶
 - (1) Urinary excretion
 - (2) Muscle content
 - b Diuresis on the administration of desiccated thyroid¹³⁸
- 3 Sugar (blood) decreased due to lowered
 - a Liver function
 - b Intestinal absorption
- 4 Cholesterol (plasma) is increased
- 5 Protein in
 - Spinal fluid is increased
 - b Exudates may occur in all serous cavities

C ALTERATIONS IN BODY ORGANS AND TISSUES

- 1 Liver function is decreased as reflected by hypercholesterolemia due to a backlog of undistributed ingested cholesterol which can be lowered by diet and without thyroid medication (see Chart 42)
- 2 Pituitary thyrotropin
 - a Hypersecretion of this hormone is the only known increased function of the body
 - b Cells producing it may be affected ultimately by the lack of thyroid hormone
- 3 Adrenals
 - a Less active if the decreased 17 ketosteroid output is an index of such a function (see 25 VII F5)
 - b Hypothyroid patients respond less to adrenalin and ACTH
- 4 The following activities are decreased
 - a Central as well as sympathetic nervous system
 - b Circulatory
 - c Hematopoietic for normocytic (common) or hypochromic anemia indicates the sluggishness of bone marrow response
 - d Gastro intestinal
- 5 Cellular functions
 - a Alteration of
 - (1) Membrane permeability
 - (2) Electrophysical reactions
 - b Intracellular fluid increased
 - c Laying down of extracellular substances of
 - (1) Water
 - (2) Mucin
 - d Reduction of (voluntary and involuntary)
 - (1) Muscular strength
 - (2) Irritability

XIII DIAGNOSIS

A GENERAL

- 1 Mental processes retarded
- 2 Cold sensitivity
- 3 Skin—dry
- 4 Pulse rate
 - a Normal
 - b Slow
- 5 Cholesterol (plasma)—elevated
- 6 Protein (serum)—increased
- 7 Iodine (total or plasma bound)—low

- 8 Basal metabolic rate averages between minus 30 and minus 40 per cent on repeated tests

B SUMMARY

- 1 Every item of above may be within normal limits in a given case if any two are absent the diagnosis is unlikely
- 2 Satisfactory therapeutic response (except for anginal symptoms) on usual thyroid dosage (not over 2 gr a day)
- 3 If patient is taking thyroid
 - a Medication should be stopped
 - b Basal metabolic rate and cholesterol (plasma) are determined in 2 or 3 weeks
 - c Definite clinical signs may not appear for 1 to 3 months⁷

XIV DIFFERENTIAL DIAGNOSIS

A OBESITY

- 1 This is not an important diagnostic sign of myxedema although patients may be
 - a Overweight—60 per cent
 - b Normal or underweight—40 per cent¹
- 2 Absence of
 - a Dry skin
 - b Nonpitting edema
 - c Hair changes
 - d Cold sensitivity
 - e Mental retardation
- 3 Cholesterol (plasma)—normal
- 4 Iodine (blood)—normal

B HYPOMETABOLISM (as for obesity)¹⁻³

C CHRONIC FATIGUE (as for obesity)

D SENILITY (as for obesity)

E CHRONIC NEPHRITIS

- 1 Retinitis—uncommon in myxedema
- 2 Pitting edema—present
- 3 Albuminuria—excessive
- 4 Protein (serum)
 - a Decreased (most unusual in myxedema)
 - b Reversal of albumin globulin ratio

F HYPOPITUITARISM OR SIMMONDS DISEASE

- 1 Skin is smooth (see 4 VI E 5 VI E)
- 2 Pubic and axillary hair are absent
- 3 Weight loss is common
- 4 Mental lethargy rarely found
- 5 Menorrhagia is absent
- 6 Cholesterol (plasma) averages are lower

- 7 Electrocardiogram is more frequently normal

- 8 Pituitary tumor may be present

G OTHER CONDITIONS

- 1 A variety of other clinical states may raise the question of myxedema, on the other hand, many of the changes found in hypothyroidism may suggest other entities, for example
 - a Cushing's syndrome
 - b Angina pectoris
 - c Congestive heart failure
 - d Pernicious anemia
 - e Mental disorders
 - f Simple constipation
- 2 Hypercholesterolemia is often found in (see 14 VIII D 1, 103 III I 2)
 - a Diabetes mellitus (in acidosis)
 - b Some otherwise normal people
 - c Old age
 - d Some cases of coronary arteriosclerosis
 - e Nephrosis
 - f Common duct obstruction
 - g Xantheloma or xanthelasma

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A CARDIAC COMPLICATIONS (see Charts 43 and 44 Figs 178 and 179)³⁰

- 1 Angina of effort may be due to
 - a Coronary sclerosis
 - b Anoxia possibly
 - c Cardiac muscle damage (see 2b \ B 3)
- 2 Coronary infarction⁸
- 3 Congestive heart failure
- 4 Polyserous effusions are not solely due to congestion
- 5 Hypertension
- 6 Coincidental cardiovascular disease

II ASSOCIATED DISEASES

- 1 Hyperparathyroidism⁸
- 2 Diabetes^{81 130}
 - a Association with hypothyroidism—rare
 - b If myxedematous condition in proves diabetes becomes worse and vice versa
- 3 Xanthoma tuberosum
- 4 Arteriosclerosis
- 5 Vitamin deficiencies
- 6 Pernicious anemia¹³ & 100 115

XVI TREATMENT

A MEDICATION

1 Desiccated thyroid (USP)

a Dosage	GR DAILY
(1) Initial	$\frac{1}{2}$
(2) After several weeks	1
(3) Final	$1\frac{1}{2}$ 2
(4) Maximal or optimal	2

II Caution

(1) An initial large dose may invoke status anginosus and should be avoided (see Fig 181)

(2) Overdosage may cause symptoms of hyperthyroidism (see 26 VII)

III Cholesterol (plasma) and metabolic determinations are useful, but often optimal dose is learned by patient

2 Drug tolerance

a Sensitivity (marked) to

- (1) Morphine
- (2) Barbiturates

b Adrenalin responsiveness is decreased

B MANAGEMENT

1 Obesity—reduction diet should be advised rather than larger doses of thyroid

2 Anemia

a Primary—liver

b Secondary—iron

(1) Doubtful benefit if primarily due to myxedema

(2) Look for other causes if not corrected after 3 months of adequate thyroid treatment

3 Arthritis

a Analgesics

b Physiotherapy

c Orthopedic measures

C RESULTS

1 Cardiovascular system (see Fig 181)

a Angina pectoris may

(1) Disappear possibly due to muscle change rather than to coronary arteries

(2) Become worse probably because of coronary insufficiency

b Coronary thrombosis or infarction may occur during therapy

c Congestive failure may

(1) Respond to desiccated thyroid alone (see Chart 44)

(2) Improve with removal of fluids suggesting mechanical embarrasment as an important factor

d Electrocardiogram

(1) Reversion to normal usually (see Fig 173)

(2) If due to an associated organic disease may not revert to normal especially if bundle branch block

e Cardiac size regresses to normal unless previous hypertrophy was present (see Figs 174 178)

2 General outcome (see Fig 182)

a Improvement in

(1) Body and mental sluggishness

(2) Hair growth unless too old

(3) Skin

(a) Texture

(b) Moisture

(4) Gastrointestinal complaints although this is not always striking

(5) Gonadal dysfunction

(6) Joint stiffness

b Urinary and blood changes

(1) Cholesterol (plasma) decreases to normal unless too high, i.e. over 600 mg % (see Chart 42)

(2) Protein reverts to normal

(3) Increase usually, in

(a) Creatinuria

(b) Iodine (blood and urine)

(c) Hemoglobin

(d) 17 ketosteroids

c Basal metabolic rate becomes normal

D COMPLICATIONS

1 If large or maintenance doses are given initially the following may develop

a Angina or status anginosus

b Coronary infarction

c Palpitation

d Dyspnea

e Apprehension

f Muscular or bone

(1) Pain

(2) Cramps

g Mental aberrations

h Acute psychosis

i Vertigo

j Weakness

k Sudoresis

E. SURGICAL

- 1 Indication—removal of adenomatous goiter when associated with myxedema
- 2 Preparation—thyroid should be given preoperatively to relieve myxedema
- 3 Results
 - a Striking reduction in size of goiter may occur
 - b Removal of a large, nodular and distended goiter might bring about a return of normal thyroid function

61 67 67

XVII PROGNOSIS

A. GENERAL

- 1 Without treatment—estimated life span is from 10 to 15 years

2 With treatment

- a Good outlook apparently
- b If coronary artery disease is present patient may actually be better with out treatment, although this cannot be proved

XVIII CAUSES OF DEATH

A. SUMMARY

- 1 Myxedematous coma, if not treated
- 2 Coronary
 - a Thrombosis
 - b Infarction
- 3 Status anginosus from overtreatment
- 4 Infections
- 5 Cerebral vascular accidents
- 6 Miscellaneous

REFERENCES

- 1 Abrams M I and Gilligan D R Carbohydrate metabolism in human hypothyroidism induced by total ablation of thyroid gland blood sugar response to insulin *Am J M Sc* 188 796 800 (Dec) 1934
- 2 Asher R Myxedematous madness *Brit M J* 2 555 562 (Sept) 1949
- 3 Aub J C Bauer W Heath C and Ropes M Studies of calcium and phosphorus metabolism effects of thyroid hormone and thyroid disease *J Clin Investigation* 7 97 137 (Apr) 1929
- 4 Aub J C Bauer W Ropes M and Heath C Relation of thyroid gland to calcium metabolism *Tr A Am Physicians* 42 344 1927
- 5 Althausen T I Lockhart J C and Soley M H New diagnostic test (galactose) for thyroid disease *Am J M Sc* 199 342 351 (Mar) 1940
- 6 Bartels H C and Bell G Myxedema and coronary sclerotic heart disease *Tr Am A Study Goiter* 1939 pp 5 15
- 7 Bartels E C Profound myxedema with normal plasma cholesterol *Lahey Clin Bull* 5 137 142 (July) 1947
- 8 Bassett A M Coons A H and Salter W T Protein bound iodine in blood naturally occurring iodine fractions and their chemical behavior *Am J M Sc* 202 516 527 (Oct) 1941
- 9 Beaumont G E and Pobert on J D Renal function in myxedema *Brit M J* 2 578 (Nov) 1943
- 10 Bence J and Engel K Ueber Veränderung des Blutbildes bei Myxodema *Wien klin Wchnschr* 21 905 1908
- 11 Beumer H and Iseke C Der Kreatin-kreatininstoffwechsel bei Myxodem und Geunden unter Einwirkung von Thyreoidin *Berlin klin Wchnschr* 57 178 181 (Feb) 1920
- 12 Biedl A Innere Sekretion ed 2 Berlin Urban 1913 p 170
- 13 Bomford R Anaemia in myxedema and role of thyroid gland in erythropoiesis *Quart J Med* 7 495 536 (Oct) 1938
- 14 Boothby W M Sandiford I Sandiford K and Slosse J The effect of thyroxin on the respiration and nitrogenous metabolism of normal and myxedematous subjects *Tr A Am Physicians* 40 195 229 1925
- 15 Boyd E M and Connell W F Plasma lipids in diagnosis of mild hypothyroidism *Quart J Med* 8 467-471 (Oct) 1937
- 16 Bramwell H The clinical features of myxoedema *Edinburgh M J* 38 985 995 1892
- 17 Byrom F B The nature of myxedema *Clin Sc* 1 273 285 (Nov) 1934
- 18 Collip J B Corticotrophic (adrenotropic) thyrotrophic and parathyrotrophic factors *JAMA* 115 2073 2079 (Dec) 1940
- 19 Cope C L Anterior pituitary lobe in Graves disease and in myxoedema *Quart J Med* 7 151 160 (Jan) 1938
- 20 Craig L S Luser H and Soley M H Report of two cases of myxedema with extreme hypercholesteremia one complicated by xanthoma tuberosum *J Clin Endocrinol* 4 12 16 (Jan) 1944
- 21 Curtis G M Iodine relationships of thyroid disease *Surg Gynec & Obst* 62 365 372 (Feb) 1936
- 22 Curtis G M and Cole V V The blood iodine in thyroid disease *Tr Am A Study Goiter* 1934 pp 142 155
- 23 Curtis G M Davis C B and Phillips F J Significance of iodine content of human blood *JAMA* 101 901 905 (Sept) 1933
- 24 Curtis G M Cole V V and Phillips F J The blood iodine in thyroid disease *West J Surg* 42 435 448 (Aug) 1934
- 25 Decourt J Le rôle du corps thyroïde dans la régulation de la chlorémie *Ann de méd.* 44 133 144 (July) 1938
- 26 Deuch G Blood in myxedema *Deutsches Arch f klin Med* 134 342 (Dec) 1970
- 27 Dine R F and Lavietes P H Serum magnesium in thyroid disease *J Clin Investigation* 21 781 786 (Nov) 1942

- 28 Eichhorst H Über Veränderungen in der Hypophyse cerebri bei Kretinismus und Myxo dem Deutsches Arch f klin Med 124 207 270 (Dec) 1917
- 29 Eisler B and Schittenhelm A Action of thyroxin on the blood iodine in myxedema Ztschr f d ges exper Med 68 487-492 1929
- 30 Elmer A W Iodine tolerance test for thyroid insufficiency Endocrinology 18 487 496 (July Aug) 1934
- 31 Emerson K Jr and Cutting W C Urinary thyrotropic hormone Endocrinology 23 439 445 (Oct) 1938
- 32 Emery E S Jr Blood in myxedema Am J M Sc 165 577 583 (Apr) 1923
- 33 Engstrom W W and Mason H L Excretion of 17 ketosteroids in patients with hyperthyroidism and myxedema J Clin Endocrinol 4 517 527 (Nov) 1944
- 34 Erdheim J Medionecrosis aortae idiopathica cystica Virchows Arch f path Anat 276 187 229 1930
- 35 Escamilla R F Carotinemia in myxedema explanation of typical slightly icteric tint J Clin Endocrinol 2 33 35 (Jan) 1942
- 36 — Diagnostic significance of urinary hormonal assays report of experience with measurements of 17 keto steroids and follicle stimulating hormone in the urine Ann Int Med 30 249 290 (Feb) 1949
- 37 Escamilla R F, Lusser H and Shepardson H C Internal myxedema report of case showing ascites cardiac intestinal and bladder atony menorrhagia secondary anemia and associated carotinemia Ann Int Med 9 297 316 (Sept) 1935
- 38 Evans W A case of myxedema with ascites and atony of the urinary bladder Endocrinology 16 409-416 (July Aug) 1932
- 39 Fahr G Myxedema heart report based upon study of 17 cases of myxedema Am Heart J 8 91 101 (Oct) 1932
- 40 Falta Wilhelm The Ductless Glandular Diseases translated and edited by M K Meyers Philadelphia Blakiston 1915 p 112
- 41 Fellinger K Klinische und experimentelle Untersuchungen über das Verhalten und die Bedeutung des thyreotropen Hormons im Blute Wien Arch f inn Med 29 375 406 1936
- 42 Fitz R and Hunt H S Experiences with iodine tolerance test in hypothyroid patients Tr A Am Physicians 52 24 25 1937
- 43 Forbes A F Griswold G C and Albright F Clinical experience with a bioassay method for the determination of urinary corticosteroids J Clin Endocrinol 10 230 247 (Feb) 1950
- 44 Foster M and Barr M P Myxedema record of autopsied case with special emphasis upon lesions of muscles J Clin Endocrinol 4 417 426 (Sept) 1944
- 45 Fraser R W Albright F and Smith P H Value of glucose tolerance test insulin tolerance test in diagnosis of endocrinologic disorders of glucose metabolism J Clin Endocrinol 1 297 306 (Apr) 1941
- 46 Fraser R W Forbes A P Albright F Sulzowitch H and Reifsenstein E Colorimetric assay of 17 keto steroids in urine survey of use of this test in endocrine investigation diagnosis and therapy J Clin Endocrinol 1 234 256 (Mar) 1941
- 47 Fraser R and Smith P H Summons disease or panhypopituitarism (anterior) its clinical diagnosis by combined use of 2 objective tests Quart J Med III 297 330 (Oct) 1941
- 48 Freeman E H Chronic pericardial effusion in myxedema report of case Ann Int Med 7 1070-1079 (Mar) 1934
- 49 Friedgood II B On the physiological significance of the abnormally decreased or absent 17 ketosteroid excretion in Addison's disease panhypopituitarism and myxedema Federation Proc 1 26 27 (Mar) 1942
- 50 Gardiner Hill H Brett P C and Smith J F Carbohydrate tolerance in myxoedema Quart J Med III 327 334 (Apr) 1925
- 51 Gildea H F Man E B and Peters J F Serum lipoids and proteins in hypothyroidism J Clin Investigation III 739 755 (Nov) 1939
- 52 Giligan D R Abrams M I and Stern B Carbohydrate metabolism in human hypothyroidism induced by total thyroidectomy glucose tolerance curve and fasting serum sugar concentration Am J M Sc 188 790 796 (Dec) 1934
- 53 Glass S J Case of myxedema with macrocytic anemia successfully treated with thyroid and testosterone J Clin Endocrinol 3 421 425 (July) 1943
- 54 Golding F C Association of atrophic gastritis with hypothyroidism preliminary report of 11 cases Ann Int Med 17 828 834 (Nov) 1942
- 55 Gordon A H Pericardial effusion in myxedema Tr A Am Physicians 50 272 277 (May) 1935
- 56 — Some clinical aspects of hypothyroidism Canad M A J 20 7 10 (Jan) 1929
- 57 Gray H Blood sugar standards in conditions neither normal nor diabetic Arch Int Med 31 259 262 (Feb) 1923
- 58 Green A M Iodine and cholesterol metabolism in patients with primary myxedema clinical and experimental study with report of results of treatment Arch Int Med 67 114 128 (Jan) 1941
- 59 Haussen P Myxedema and ascites Acta med Scandinav Suppl VII 275 287 1938
- 60 Heckscher H Untersuchungen über den Fett Cholesterin Gehalt des Blutes bei thyreoideotomierten Pferden Biochem Ztschr 158 417 421 (Mar) 1925
- 61 — Über die Fett Cholesterin Menge des Blutes bei Kretinen Biochem Ztschr 158 422-427 (Mar) 1925
- 62 Hertz J On Goutre and Allied Diseases Especially Thyrotoxicosis Copenhagen Munksgaard London Oxford 1943 p 193
- 63 Hertz S and Ostler E G Assay of blood and urine for thyreotropic hormone in thyrotoxicosis and myxedema Endocrinology 20 520-525 (July) 1936
- 64 Hertzler A E Diseases of the Thyroid Gland Presenting the Experience of More Than Forty Years New York Hoeber 1941 p 670
- 65 Holst J Bemerkungen zur pathologischen Physiologie der Strumen Ber u d Internatnalen Kropfkongferenz Bern Aug 24 26 1927
- 66 Horsely V The thyroid gland its relation to the pathology of myxoedema and cretinism to the question of the surgical treatment of goitre and to the general nutrition of the body Brit M J 1 111 115 211 213 1885

- 67 Hotz G Zur Kropffrage Schweiz med Wchnschr 2 1153 1154 (Dec) 1921
- 68 Howard C P Myxedema a study JAMA 48 1226 1403 1907
- 69 Howell L P The excretion of gonadotropic principle in thyroid disease Tr Am A Study Gouter 1940 pp 157 159
- 70 Howell L P Drips D G and Fisher H C Presence of excessive amounts of gonadotropic principle in urine of patients with thyroid disease Am J Obst & Gynec 41 868 873 (May) 1941
- 71 Hun H and Prudden T M Myxedema four cases with two autopsies with a report of the microscopical examination Am J M Sc 96 1 140 1858
- 72 Hurxthal L M Unpublished data
- 73 — Blood cholesterol in thyroid disease analysis of findings in toxic and nontoxic goiter before treatment Arch Int Med 51 72 32 (Jan) 1933
- 74 — Blood cholesterol and thyroid disease myxedema and hypercholesteremia Arch Int Med 53 762 781 (May) 1934
- 75 — Myxedema heart with congestive heart failure and polyserous effusions New England J Med 213 264 267 (Aug) 1935
- 76 Hurxthal L M and Hunt H M Clinical relationships of blood cholesterol with summary of our present knowledge of cholesterol metabolism Ann Int Med 9 717 727 (Dec) 1935
- 77 Hurxthal L M and Musulin N Hypertrophic chosis and myxedema Lahey Clin Bull 4 102 110 (Apr) 1945
- 78 Hurxthal L M and Perkins H J Fractionation of iodine of blood in thyroid disease J Clin Investigation 18 733 737 (Nov) 1937
- 79 Hurxthal L M and Simpson H N Hypothyroidism hypercholesterolemia J Clin Endocrinol 1 450 457 (May) 1941
- 80 Janney N W and Henderson H E Concerning diagnosis and treatment of hypothyroidism Arch Int Med 26 297 (Sept) 1920
- 81 Janney N W and Isaacson V I Blood sugar in endocrine disease Arch Int Med 22 160 (Aug) 1918
- 82 Jones R M Human sternal bone marrow in hyperthyroid and myxedematous states Am J M Sc 200 11 220 (Aug) 1940
- 83 Jones M S Study of thyrotropic hormone in clinical states Endocrinology 24 665 671 (May) 1939
- 84 Joslin E P Root H F White P Marble A and Bailey C C Treatment of Diabetes Mellitus Philadelphia Lea & Febiger 1937 p 581
- 85 Kassin M and Bakst H Co existing myxedema and hyperparathyroidism case report J Clin Endocrinol 7 152 158 (Feb) 1947
- 86 Kniefelder H F Jr Albright F and Griswold G C Experience with quantitative test for normal or decreased amounts of follicle stimulating hormone in urine in endocrinological diagnosis J Clin Endocrinol 3 529 544 (Oct) 1943
- 87 Knopfmacher W Alimentäre Glykosurie und Myxodem Wien klin Wchnschr 17 244 247 1904
- 88 Kocher T Das Blutbild bei Cachexia thyreoidea (Myxodem Cretinoid Zustände) Arch f klin Chl 99 280 303 1912
- 89 Kraepelin E Ueber Myxodem Deutsches Arch f klin Med 49 587 603, 1891 2
- 90 Lange K Capillary permeability in myxedema Am J M Sc 208 5 15 (July) 1944
- 91 Langston W Glucose tolerance test, J Lab & Clin Med 7 293 298 (Feb) 1922
- 92 Leichtenstern O Zur Geschichte der Myxodemfrage Deutsche med Wchnschr 20 251 1894
- 93 Lerman J and Brogan A J Renal function in exophthalmic goiter and myxedema Endocrinology 16 251 256 (May June) 1932
- 94 Lerman J Clark R J and Means J H Heart in myxedema electrocardiograms and roentgen ray measurements before and after therapy Ann Int Med 6 1251 1271 (Apr) 1933
- 95 — Further observations on heart in myxedema Ann Int Med 8 82 84 (July) 1934
- 96 Lerman J and Means J H Gastric secretion in exophthalmic goitre and myxedema J Clin Investigation 11 167 182 (Jan) 1932
- 97 Levy M S, Power M H and Kepler E J Specificity of water test as diagnostic procedure in Addison's disease J Clin Endocrinol 5 607 632 (Sept) 1945
- 98 Lewis L A and McCullagh E P Electrophoretic analysis of plasma proteins in hyperthyroidism and hypothyroidism Am J M Sc 208 727 735 (Dec) 1944
- 99 Lissner H Sexual infantilism of hypothyroid origin J Clin Endocrinol 2 29 32 (Jan) 1942
- 100 Lissner H and Anderson E M Three cases of adult myxedema in women reported for purpose of calling attention to their widely different symptomatology and clinical findings Endocrinology 15 365 381 (Sept Oct) 1931
- 101 Lowenstein B E Bruger M and Hinton J W Protein bound plasma iodine in patients with thyroid disease correlation with basal heat production J Clin Endocrinol 4 268 272 (June) 1944
- 102 Marine D and Rosen S H Urinary excretion of capon comb growth promoting substances in Graves disease and myxedema and modification following iodine and denervated thyroid therapy J Mt Sinai Ho p 8 811 819 (Jan Feb) 1942
- 103 Marsh H E Myxedematous ascites removed by thyroid extract Am J M Sc 172 585 588 (Oct) 1926
- 104 Marzullo E R and Franco S Myxedema with multiple serous effusions and cardiac involvement (myxedema heart) case report Am Heart J 17 368 374 (Mar) 1939
- 105 Mason R L Hunt H M and Hurxthal L M Blood cholesterol values in hyperthyroidism and hypothyroidism—their significance New England J Med 203 1273 1278 (Dec) 1930
- 106 McCullagh E P and Dunlap J H Blood picture in hyperthyroidism and in hypothyroidism J Lab & Clin Med 17 1060 1070 (July) 1932
- 107 McCullagh E P and McCullagh D W Clinical experiences in the use of determinations of blood iodine Arch Int Med 57 1061 1066 (June) 1936
- 108 McGavack T H Lanoe K and Schwimmer D Management of myxedematous patient with symptoms of cardiovascular disease Am Heart J 29 421 439 (Apr) 1945
- 109 McGavack T H and Schwimmer D Prob

- lems in treatment of cardiac failure in myxedema *J Clin Endocrinol* 4 427-439 (Sept) 1944
- 110 Means J H Diseases of thyroid gland New England *J Med* 221 820-825 (Nov) 1939
- 111 — The Thyroid and Its Diseases Philadelphia Lippincott 1937 p 199
- 112 *Ibid* p 200
- 113 *Ibid* p 222
- 114 — Hypothyroid heart disease New England *J Med* 208 541-543 (Mar) 1933
- 115 Means J H Lerman J and Castle W B The coexistence of myxedema and pernicious anemia *Tr A Am Physicians* 45 363-374 1930
- 116 Mendel E Ein Fall von Myxodem Deutsche med Wchnschr 19 25 1893
- 117 Minot G R Two curable cases of anemia *M Clin North America* 4 1 33 (May) 1971
- 118 Musso Journet J C Cervino J M and Bazzano J J Myxedematous dropsy report on case of myxedema with congestive heart failure and serous effusions with high protein content *J Clin Endocrinol* 6 758-765 (Nov) 1946
- 119 Naegele O Über die Beziehungen zwischen Störungen der innersekretorischen Organe und Blutveränderungen *Folia haemat* 25 3 13 1919
- 120 Perkin H J Brown B R and Lang J Blood iodine content of normal and thyrotropic individuals Iodine tolerance test *Canad M A J* 31 365-368 (Oct) 1934
- 121 Perkin H J and Lahey F H Level of iodine in blood *Arch Int Med* 65 832-805 (May) 1940
- 122 Perkin H J Lahey F H and Cattell R B Blood iodine in relation to thyroid disease basic concept of relation of iodine to thyroid gland iodine tolerance test New England *J Med* 214 45-52 (Jan) 1936
- 123 Peters J P and Mann M H Interrelations of serum lipids in patients with thyroid disease *J Clin Investigation* 22 715-720 (Sept) 1943
- 124 Pitfield R L Myxedema *Am J Med* 151 409 1916
- 125 Plummer W A Body weight in spontaneous myxedema *Tr Am A Study Goster* 1940 pp 83-98
- 126 Poncher H G Vuscher M B and Woodward H Creatine metabolism in children with hypothyroidism *JAMA* 102 1132-1133 (Apr) 1934
- 127 Proger S and Brauns W H Myxedema following iodine treatment for hyperthyroidism *Bull New England M Center* 5 42-47 (Feb) 1943
- 128 Puppel I D and Curtis G M Calcium and iodine metabolism in thyroid disease *Arch Int Med* 58 957-977 (Dec) 1936
- 129 Rawson H W and Starr P Direct measurement of height of thyroid epithelium method of assay of thyrotropic substance clinical application *Arch Int Med* 61 726-738 (May) 1938
- 130 Reiss R S, Pugs D H, Thora G W and Forsham P H The Adrenal Thyroid Relationship The First Clinical ACTH Conference Philadelphia Blakiston 1950 pp 193-210
- 131 Reuter M J Histopathology of skin in myxedema *Arch Dermat & Syph* 24 53-71 (July) 1931
- 132 Riggs D S, Man H B and Winkler A W Serum iodine of euthyroid subjects treated with desiccated thyroid *J Clin Investigation* 24 712-735 (Sept) 1945
- 133 Robertson J D Calcium and phosphorus excretion in thyrotoxicosis and myxedema *Lancet* 1 672-675 (June) 1942
- 134 Rolleston H D The Endocrine Organs in Health and Disease London Oxford 1936 p 521
- 135 Ross D A and Schwab H S The cortical alpha rhythm in thyroid disease *Endocrinology* 25 75-79 (July) 1939
- 136 Salter W T Endocrine Function of Iodine Harvard Monographs 1940 pp 13-19
- 137 Salter W T, Bassett A M and Sappington T S Protein bound iodine in blood its relation to thyroid function in 100 clinical cases *Am J M Sc* 202 577-582 (Oct) 1941
- 138 Schittenhelm A Schilddrüsenproblem und Jodstoffwechsel Deutsche med Wchnschr 58 803-806 (May) 1932
- 139 Shephardson H C and Weaver H A Myxedema and diabetes mellitus with report of case *Internat Clin* 4 132-133 (Dec) 1934
- 140 Shuer J W A study of serum protein in hyperthyroidism *Trans Am Assn Study of Goster* 1912 pp 89-108
- 141 Short E, Richardson H B and Mansfield J S Influence of thyroid administration on creatin metabolism in myxedema of adults *Proc Soc Exper Biol & Med* 32 1340-1342 (May) 1935
- 142 Short E, Richardson H B and Wolff H G Nature of muscular weakness in Graves disease *J Clin Investigation* 12 966-967 (May) 1933
- 143 Smith M C, Jondahl W and Ochsner A Significance of galactose tolerance test in hyperthyroidism *Surg Gynec & Obst* 74 1083-1086 (June) 1942
- 144 Spence A W Hyperthyroidism and thyrotropic hormone of the pituitary *Brit M J* 1 1277 (June) 1937
- 145 Steenstam T Petoral and intravenous galactose tests comparative study of their significance in different conditions *Acta med Scandinav* (Suppl 177) p 74 1946
- 146 Stephens D J Chloride excretion in hypothyroidism *Proc Soc Exper Biol & Med* 43 742-744 (Apr) 1940
- 147 Stewart H J and Evans W F Peripheral blood flow in myxedema *Arch Int Med* 69 808-811 (May) 1947
- 148 Stokes E H The Blood Cholesterol Content in Myxedema and Other Conditions Sydney Australia New Pub Co 1941
- 149 Talbot N B, Albright F, Salzman A H, Zygmuntowicz A and Watson R The excretion of 11 oxy corticosteroid like substances by normal and abnormal subjects *J Clin Endocrinol* 7 331-351 (May) 1947
- 150 Thompson W G Report of a case of myxedema *Tr A Am Physicians* 8 372-379 1893
- 151 Thompson W Q Studies in blood volume blood volume in myxedema with comparison of plasma volume changes in myxedema and cardiac edema *J Clin Investigation* 2 477-520 (Aug) 1926
- 152 Thompson W Q, Thompson H F, Silveus E and Dailey M E Protein content of cerebro

- spinal fluid in myxedema *J Clin Investigation* 6 251 255 (Oct) 1928
- 153 — Cerebrospinal fluid in myxedema *Arch Int Med* 44 368 373 (Sept) 1929
- 154 Thorn G W Creatine studies in thyroid disorders *Endocrinology* 20 628 634 (Sept) 1936
- 155 Thurmon F W and Thompson W O Low basal metabolism without myxedema *Arch Int Med* 46 879 887 (Nov) 1930
- 156 Tierney N A and Peters J P Mode of excretion of creatine and creatine metabolism in thyroid disease *J Clin Investigation* 22 595 607 (July) 1943
- 157 Trucco E Carotenos e insuficiencia tiroidea *Medicina Buenos Aires* 5 400 415 (July) 1945
- 158 Turner K B DeLamater A and Province W D Observations on blood iodine blood iodine in health in thyroid and cardiorenal disease and in leukemia *J Clin Investigation* 19 515 524 (May) 1940
- 159 Turner R G and Matthews C W Iodine content of blood in certain pathological conditions *J Biol Chem* 92 88 (June) 1931
- 160 Veil W H and Sturm A Iodine metabolism *Deut.ches Arch f Klin Med* 147 166-223 (May) 1925
- 161 Watson C J Crag D and Beach N Myxedematous ascites *Internat Clin* 4 176 182 (Dec) 1941
- 162 Watson E M Relation of iodine tolerance to thyroid function *Endocrinology* 23 578 537 (May) 1938
- 163 — Iodine tolerance test for investigation of thyroid function *Endocrinology* 20 353 362 (May) 1936
- 164 White W H A clinical lecture on myxedema *Lancet* 1 154 157 1913
- 165 Wilder R M and Sansum W D Glucose tolerance *Arch Int Med* 19 311 (Feb) 1914
- 166 Wilkins L W and Fleischmann T W Effects of thyroid on creatine metabolism with a discussion of mechanism of storage and excretion of creatine bodies *J Clin Investigation* 23 360 377 (May) 1946
- 167 Winkler A W Rings D S and Van E B Serum iodine in hypothyroidism before and during thyroid therapy *J Clin Invest* 24 732 741 (Sept) 1945



FIG 168 MYXEDEMA (*Left*) Classical myxedema (*Right*) Atypical appearance in myxedema Mentally sluggish Dry skin Plasma cholesterol 200 mg % BMR minus 20% Pulse 58 Administration of 1 gr desiccated thyroid Plasma cholesterol 200 mg % BMR \pm 0% Relief of symptoms (Hurxthal L M Myxedema The Cyclopaedia of Medicine (Piersol) Philadelphia, Davis pp 119 131)



FIG 169 MYXEDEMA in a nonobese woman Note sparsity of hair on head (*Left*) Before treatment (*Right*) After 3 months of desiccated thyroid orally Observe change in facial expression regrowth of hair and loss of bloaty appearance



FIG 170 MYXEDEMATOUS SKIN



FIG 171 MYXEDEMA Loss of head hair in myxedema and regrowth with treatment by desiccated thyroid



FIG 172 MYXEDEMA Age 28 Chief complaints dyspnea for over a year and angina of effort BP 110/10 Vital capacity 2 300 cc Excess hair on face neck arms and chest was noted 1 year before Female escutcheon Weight 148 lbs Plasma cholesterol 416 mg % BMR minus 33% Age 29 Weight 129 lbs BP 110/80 Patient taking 12 gr of desiccated thyroid per week Hair decreased in amount 17 ketosteroids on treatment were 5.8 and 6.5 mg/24 hrs Angina of effort relieved (Left) Photo taken 1 month after beginning of treatment with desiccated thyroid (initial photograph was lost) (Right) Five months later Note loss of hair on edge of forehead under chin and between and around eyebrows

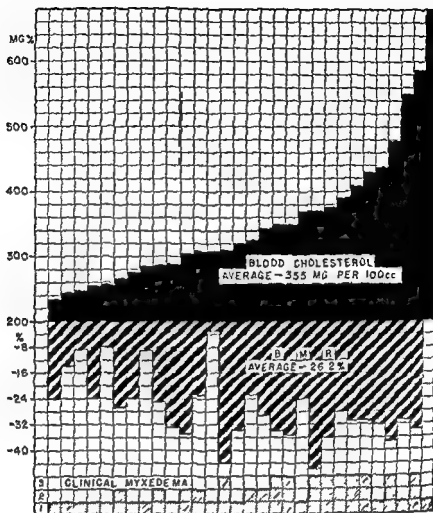


CHART 40 MYXEDEMA Variation in plasma cholesterol and BMR in 30 cases of spontaneous myxedema. Note that myxedema may be present with relatively little elevation of plasma cholesterol and occasionally with a normal BMR at least on first test. In the last case with the very high cholesterol only one BMR could be obtained. When myxedema was completely relieved plasma cholesterol was 300 mg % suggesting that myxedema was superimposed on an individual with idiopathic hypercholesterolemia. The shaded areas below depict the grade of myxedema as judged from physical findings (Hurxthal L M Blood cholesterol and thyroid disease. III Myxedema and hypercholesterolemia Arch Int Med 53 762-781)

CHART 41 MYXEDEMA Age 65 female Effect of low cholesterol diet on plasma cholesterol in myxedema with angina pectoris Thyroid could not be tolerated in $\frac{1}{4}$ gr daily doses and low cholesterol diet was tiresome No clinical improvement Hypertension

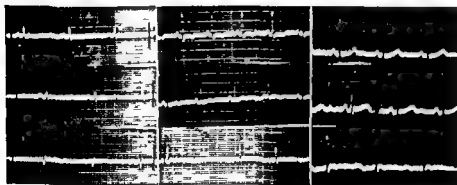
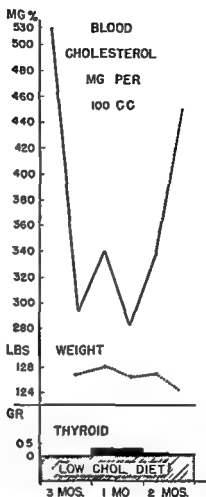


FIG 173 MYXEDEMA HEART WITH CONGESTIVE HEART FAILURE (See also Fig 178) Electrocardiograms taken before 10 days and 14 days after treatment Thyroxin given orally (Huxthal L M Myxedema heart with congestive heart failure and polyserosal effusions New England J Med 213 264 267)



FIG 174 MYXEDEMA HEART Age 55 female Weight 144 lbs BP 100/80 Duration of symptoms 2 years RBC 3.9 million Hgb 10.6 Gm Hematocrit 33% Plasma cholesterol 362 mg % BMR minus 25% (Left) Heart before therapy (Right) Heart 2 months later Weight loss 9 lbs



FIG 175 MYXEDEMA Photomicrograph of thyroid gland in myxedema (See also Fig 176) Note scarring and small island of thyroid tissue remaining Follicular remnants are barely discernible Only a few of these were found on sectioning



FIG 176 MYXEDEMA Atheromatous mass due almost completely filling the coronary artery in a man with myxedema dying of coronary failure The mass occluding the artery is filled with cholesterol Only a small portion of lumen remains The black areas are calcium deposits

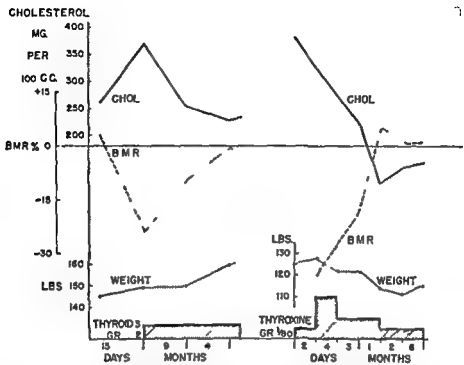


CHART 42 MYXEDEMA (Left) Age 45 female Effect of withdrawing desiccated thyroid on cholesterol BMR and weight in a patient with myxedema Physical changes may not become apparent for from 1 to 3 months (Right) Age 49 female Effect of administering thyroxin to a patient with myxedema in too large a dose Note gain in weight when thyroid was readministered (left) and inverse relationship between cholesterol and BMR The contour of the cholesterol curve is usually similar to contour of weight curve (Hurxthal L M Blood cholesterol and thyroid disease III Myxedema and hypercholesteremia Arch Int Med 53 :62 781)



FIG 177 MYXEDEMA Primary myxedema in a man of 24 complaining of fatigue Pulse was slow but no abnormality was noted in electrocardiogram

CASES

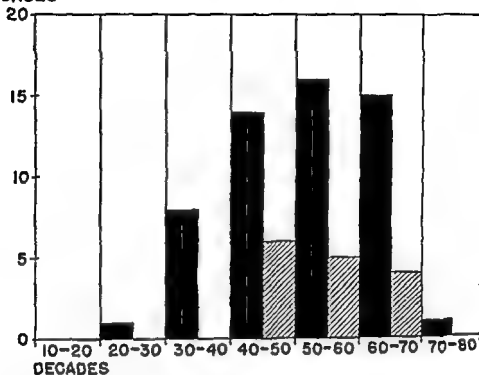


CHART 43 MYXEDEMA Age distribution in 59 cases of spontaneous myxedema (solid block) with cases manifesting evidence of coronary insufficiency i.e. angina of effort or coronary infarction (cross hatched) (Bartels E C and Bell E Myxedema and coronary sclerotic heart disease Tr Am A Study Goutier 1939 pp 5 15)



FIG 178 MYXEDEMA HEART WITH POLYSEROUS EFFUSIONS (See also Fig 173 and Chart 44) (Left) Before treatment (Right) Four weeks after treatment with thyroxin (Hurxthal L M Myxedema heart with congestive heart failure and polyserous effusions, New England J Med 213 264 267)

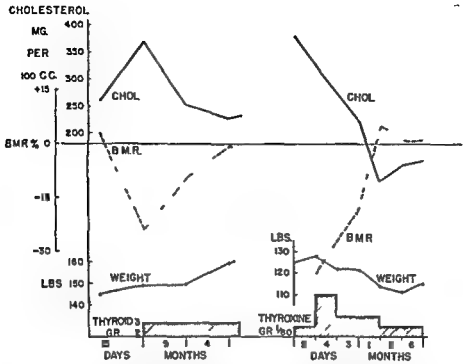


CHART 42 MYXEDEMA (*Left*) Age 45 female Effect of withdrawing desiccated thyroid on cholesterol BMR and weight in a patient with myxedema Physical changes may not become apparent for from 1 to 3 months (*Right*) Age 49 female Effect of administering thyrotoxin to a patient with myxedema in too large a dose Note gain in weight when thyroid was readministered (*left*) and inverse relationship between cholesterol and BMR The contour of the cholesterol curve is usually similar to contour of weight curve (Hurxthal L 51 Blood cholesterol and thyroid disease III Myxedema and hypercholesteremia Arch Int Med. 53 :62 781)

FIG 177 MYXEDEMA Primary myxedema in a man of 24 complaining of fatigue Pulse was slow but no abnormality was noted in electrocardiogram



CASES

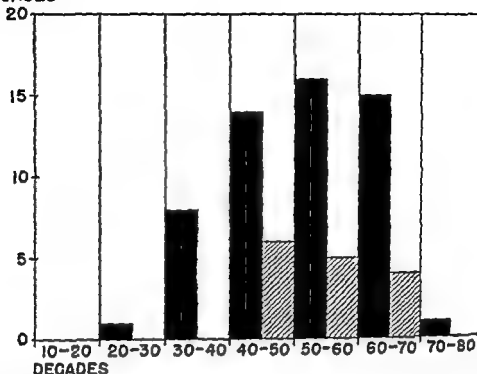


CHART 43 MYXEDEMA Age distribution in 59 cases of spontaneous myxedema (solid block) with cases manifesting evidence of coronary insufficiency, i.e. angina of effort or coronary infarction (cross hatched) (Bartels, E. C. and Bell, G. Myxedema and coronary sclerotic heart disease Tr Am A Study Goiter, 1939 pp 5-15)

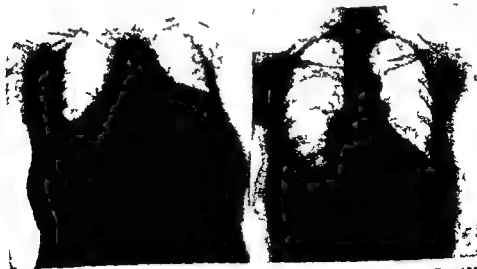


FIG 178 MYXEDEMA HEART WITH POLYMEROUS EFFUSIONS (See also Fig 173 and Chart 44) (Left) Before treatment (Right) Four weeks after treatment with thyroxin (Hurxthal, L. M. Myxedema heart with congestive heart failure and polyserous effusions New England J Med 213 264-267)

CHART 44 MYXEDEMA HEART (See also Figs 173 178) Myxedema heart with congestive heart failure and polyserous effusions. Treatment with bed rest and thyroxin 1/80 gr daily. Note diuresis as shown by loss of over 25 lbs. It was concluded that polyserous effusions were as much responsible for the pleural pericardial and abdominal fluid as congestive failure (Hurxthal L M. Myxedema heart with congestive heart failure and polyserous effusions. New England J Med 213 264 267)

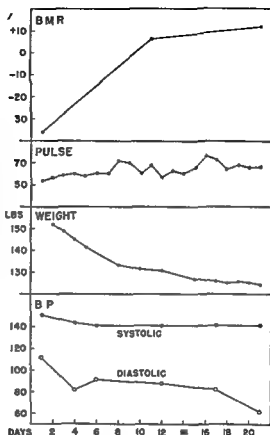


FIG 179 MYXEDEMA HEART (Left) Cardiac outline before pericardial tap (Right) After withdrawal of 450 cc of fluid. Note fluid level (arrow) (Freeman E B. Chronic pericardial effusion in myxedema. Ann Int Med 7 1070 1079)



FIG 180 PRIMARY MYXEDEMA Myxedema with aneurysm of internal carotid artery causing an enlarged sella
Age 65 BP 160/110 Plasma cholesterol 309 mg %
Adrenal water test negative Urinary FSH strongly positive 17 ketosteroids 5.2 mg/24 hrs Typical physical signs of myxedema Improved with $\frac{1}{2}$ gr desiccated thyroid Angina of effort prevented larger doses It is believed that myxedema was primary and that the aneurysm was secondary in view of negative adrenal water test which is often positive when pituitary myxedema is present

FIG 181 MYXEDEMA Age 60 Previous adenomatous goiter removed surgically (Left) Condition after discontinuing thyroid for 1 year Rather severe angina of effort (Right) After 2 months of treatment with desiccated thyroid Given first in doses of $\frac{1}{4}$ gr a day and finally 1 gr a day There was no aggravation of angina in this case in fact some apparent improvement (Note regrowth of head hair)



FIG 182 MYXEDEMA (Left) Age 47 Weight 203 lbs Plasma cholesterol 413 mg % Whole blood iodine 5.2 micrograms % BMR minus 36% (Center) After 3 weeks of treatment (Right) Age 49 Weight 165 lbs Plasma cholesterol 215 mg % Two gr of desiccated thyroid taken daily

SECTION 26

HYPERTHYROIDISM

SYNONYMS

Hypersecretory diffuse hyperplastic goiter
 Parry's disease
 Graves's disease
 Basedow's disease
 Exophthalmic goiter
 Primary hyperthyroidism
 Thyrotoxicosis
 Toxic hyperplastic goiter
 Hypersecretory nodular goiter
 Adenomatous goiter with hyperthyroidism
 Nodular goiter with hyperthyroidism
 Multiple colloid adenoma with hyperthyroidism

Toxic adenomatous goiter
 Toxic nodular goiter
 Hypersecretory solitary nodule
 Hyperfunctioning adenoma
 Hyperfunctioning solitary nodule
 Toxic adenoma
 Plummer's disease
 Mixed types
 Nodular or adenomatous goiter with superimposed Graves's disease or secondary hyperthyroidism nodular goiter and superimposed hyperplasia in remainder of gland
 Hyperthyroidism with any coincident thyroid disease

I DEFINITION

Hyperthyroidism is characterized by an excessive production of thyroid hormone with subsequent increase in all metabolic processes and usually may be identified by the following: the presence of goiter nervousness intolerance to heat excessive sweating weight loss (in spite of an adequate caloric intake) weakness fatigue tremor tachycardia an increased basal metabolic rate lowered plasma cholesterol an elevated blood iodine and creatinurea

II APPEARANCE

Normal alert or apathetic individual with a hunted expression or one of frozen fright when exophthalmos is present evidence of weight loss depending on severity and duration of the disease (see below Figs 183 187)

III AGE

A PRIMARY HYPERPLASTIC GOITER

Average 37 years (youngest $2\frac{1}{4}$ years oldest 81 years at Lahey Clinic)^{12 2,3 4}

B NODULAR GOITER

Average 49 years approximately

IV SEX

Females 88 per cent males 12 per cent

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal or above average

B RESPONSIVENESS

Quick and alert

C OTHER ABNORMALITIES

Anxious emotional intense excitability depression psychosis or delirium may be present

VI PHYSICAL STATUS

A NUTRITION

Normal or poor

1 Weight

Variable more often decreased occasionally obese (see 26 VII C)

2 Fat distribution

Normal

- B HEIGHT** Normal or slightly taller than the average, if disease occurs before epiphyseal closure,¹⁶¹⁻¹⁶³ "thyroid gigantism" has been reported¹⁶¹
- C EXTREMITIES** Normal or evidence of weight loss, muscle atrophy and tremor
- 1 Upper
- Hands Normal size and shape, may have atrophy of thenar and hypothernar surfaces
- b Fingers Normal
- Span Normal or increased
- 2 Lower Normal or evidence of weight loss and muscular atrophy (see below)
- a Feet Normal deviations
- b Toes Normal
- D SPINE** Normal, rounded or kyphotic from wedging of vertebrae in long standing cases with osteoporosis, especially in females
- E INTEGUMENT**
- 1 General
- a Texture Normal or fine, smooth
- b Temperature Warm to touch
- Moisture Excessive sweating usually
- d Eruptions Uncommon
- e Pigmentation Tanning or bronzing may occur, partly from weight loss vitiligo more frequent (see Table 16 and Fig 188)¹⁷⁸
- f Color Flushed appearance often, occasionally jaundiced redness of elbows from constant motion, marked dermatographia
- g Nails Fissures, nail bed concave or wavy, undergrooved, pigmented (see Fig 189)³⁵¹
- 2 Hair
- a Head Normal
- b Facial Normal
- c Axillary Normal or diminished³⁵²
- d Pubic Normal or diminished
- e Body Normal males tend to be less hirsute than average¹⁷⁹

TABLE 16 DIFFUSE PIGMENTATION
(BRONZING) AND VITILIGO³³

TYPE OF GOITER	NO OF CASES	NO OF CASES WITH PIGMENT	PER CENTAGE
Exophthalmic	293	42	14.3
Adenomatous without hyperthyroidism	371	2	0.5
Adenomatous with hyperthyroidism	26	4	15.3

F HEAD

- 1 Shape and size Normal
- 2 Facial expression Normal bunted or anxious when exophthalmos present appearance of "frozen fright"

3 Eyes (see Figs 190 193)

■ General

Normal or exophthalmos, unilateral or bilateral (2%), edema and/or tremor of the lids, blepharitis excessive lacrimation, ulceration of the cornea, injected conjunctivae icteric scleras (severe cases), may have paralysis of eye muscles especially the external recti or levator superior recti, photophobia Exophthalmos of definite significance occurs in about 30 per cent of cases of diffuse hyperplastic goiter and in a few cases of hyperthyroidism with clinically nodular goiter presumably due to a superimposed Graves's disease The authors have noted slight exophthalmos or lid retraction and stare in individuals taking large doses of desiccated thyroid It is possible that excess thyroid secretion from a hyperfunctioning adenoma may produce a similar change

b Signs

All few or none of these may be found

(1) Dalrymple

Widening of palpebral fissure

(2) Von Graefe

Lid lag

(3) Stellwag

Stare or infrequent blinking

(4) Jaffe

Forehead cannot be wrinkled

(5) Moebius

Lack of convergence

(6) Jellinek

Pigmentation of eyelids

(7) Gifford

Difficulty in eversion of upper eyelid

(8) Sukers

Visual fixation from extreme lateral rotation

(9) Wilder

Jerking or twitching of globe when moving eye from extreme abduction to adduction

(10) Joffroy

Absence of brow wrinkling when looking upward and with the head down

(11) Rosenbach

Fibrillary tremor of closed eyelids

(12) Kocher

If looking upward at a moving object lids move in that direction but eyeballs do not (ophthalmoplegia)

c Fundi

Normal

d Visual

■ (1) Fields

Normal

(2) Acuity

Normal or impaired

4 Ears and nose

Normal

5 Mouth and throat

a General

Normal tongue may be red smooth, and occasionally has a tremor

b Teeth

Often carious second teeth develop prematurely²⁸

c Larynx (voice)

Normal

G NECK

1 General

Normal or fullness from the enlarged thyroid (see below) veins may be seen dilated and pulsating forcefully

2 Thyroid

Uniformly enlarged hyperplastic soft to firm, nodular or large single nodule (rare), thrills and bruits common (see 14 VIII D 2)

H CHEST

Normal loss of intercostal flesh in severe cases

I HEART AND PERIPHERAL VESSELS (see 30)

1 Heart

Normal or enlarged forceful apical thrust systolic murmurs are frequent over pulmonary and apical areas aortic diastolic murmurs are always due to an associated heart lesion vital capacity reduced, holding of breath decreased³⁴

2 Rate and rhythm	Usually tachycardia and normal rhythm, auricular premature beats 3 to 4 per cent, ventricular extrasystoles are rare, paroxysmal auricular fibrillation preoperative or postoperative in from 10 to 20 per cent established auricular fibrillation in 5.8 per cent, all types of fibrillation 10 to 15 per cent ^{10 17 17}
3 Blood pressure	Variable (see Chart 52), pulse pressure increases with basal metabolic rate, paroxysmal or established true hypertension may be coexistent, percentage increase with age, ¹⁷³ usually some elevation of systolic and lowering of diastolic pressure, slapping sounds are heard as the level of diastolic pressure is approached (see 14 VIII B 6 b, Chart 46)
4 Peripheral arteries and veins	Forceful and collapsing radial pulse, easily compressed
5 Vasomotor	General cutaneous flushing, color "high"
J BREASTS	
1 Male	Normal, gynecomastia sometimes ²²⁷
2 Female	Normal, occasionally atrophic and out of proportion to general weight loss
K ABDOMEN	
1 Liver	Normal
2 Spleen	Frequently, but only slightly, enlarged
3 Hernia	Not present
4 Tumor	Not present
L GENITALIA	
1 Male	
a Penis	Normal
b Testes	Normal
c Prostate	Normal
2 Female	
a External	Normal
b Internal	Normal
M NEUROMUSCULAR	
1 Muscles	Normal, atrophy or myasthenia ³⁸ positive quadriceps test (see 14 VIII B 5 b) atrophy of thenar and/or hypothenar eminences, weakness or paralysis of ocular muscles may occur, especially external or levator superior recti generalized hypotonia is common (see Fig 195)
2 Gait	Normal or slow if weakness of muscles exists
3 Tremor	Very fine, rapid quivering of hands may involve feet and whole body (often noted in roentgenograms or photographs)
4 Body movements	Not remarkable, other than tremulous
5 Paresthesias	Present rarely
6 Reflexes	Hyperactive usually
7 Vibratory sense	Normal or decreased
N SPEECH	Rapid and lively, quick response

VII LABORATORY DATA

A URINE	Normal
1 General	

2	Special chemical analyses	
a	Sugar	Frequently (see 31)
b	Albumin	Absent
c	Nitrogen	Increased (see 26 \I) ^{129 371 370}
d	Creatine	Normal or increased excess disappears after giving iodine ^{197 703 705 709 303 307 370 376 378 379 381 383}
e	Creatinine	Normal or decreased ^{100 170 770 376 378 379 371 370}
f	Sodium	Normal
g	Potassium	Normal or increased
h	Calcium	Increased ^{14 1 35 146 170 190 19 703 301 300}
i	Phosphorus	Increased ^{14 39 146 301}
j	Chloride	Normal or increased ³³
k	Iodine	Increased may excrete from 40 to 950 gamma in urine daily depending on food iodine intake and blood level (see 103 \I C 3 c) ^{0 80 251 250}
l	Diastase	Decreased ²²⁰
m	Vitamin C	Decreased ¹⁵
n	Urobilinogen	Present if liver damage
II	HEMATOLOGY ^{100 23 776 306}	
1	Red blood cells	Normal ^{78 81 8 100 100 146 305} occasionally hyperchromic (incidence of pernicious anemia—1 9 % ³¹), hypochromic anemia ^{100 309} or polycythemia rarely ^{149 3 1 304}
2	Hemoglobin	Normal, may be reduced ^{100 184 312 309}
3	White blood cells	Variable ^{100 184 312 309}
4	Differential	Normal ^{79 8 113 100 100} monocytes increased occasion ally relative or absolute increase in lymphocytes (not diagnostic) ⁴⁹ sometimes leukopenia, ^{78 80 100 31} iodine therapy produces no changes ¹⁸⁴ or only a decrease in monocytes ²³
5	Reticulocytes	Normal ³³
6	Coagulation time	Normal or increased
7	Color index	Normal average ³¹
8	Bone marrow	Normal or myeloid hyperplasia ^{100 33}
9	Hemoconcentration	Normal ³³
C	BLOOD CHEMICAL ANALYSES	
1	Sugar	Normal or increased slightly (see 31)
2	Nonprotein nitrogen	Normal (unless associated renal failure) ³³
3	Protein (see Chart 47)	Normal or decreased ^{3 33 63 10 225 250 3 7 346}
a	Albumin	Decreased (average per cent lower than normal)
b	Globulin	Normal or increased
c	Alpha globulin	Increased
d	Other globulin fractions	No consistent change
e	A/G ratio	Normal
f	Fibrinogen	May be high
4	Uric acid	Normal
5	Cholesterol (plasma)	Usually decreased but may be normal or increased de pending on previous level not especially helpful in diag nosis (see 14 \III D 1) ^{37 173 176 223 3 4 346}
6	Sodium	Normal or decreased ^{33 220 370}
7	Potassium	Normal or increased ^{33 222}
8	Calcium	Normal may rarely be decreased or increased ^{14 35 146 177 170 44 251 703 301 300}

9 Phosphorus	Normal or increased ¹ 35 146 190 281 283 301
10 Chlorides	Normal or increased ³³ 97
11 Phosphatase	Increased (especially in severe cases) ¹⁷ 194 199
12 Iodine	Increased (total and plasma bound) (see 103 IX C) ⁷⁷ 81 84 10 ⁶ 181 217 218 226 270 271 281 9 287 31 333 365 387 ■■
13 Creatine	Normal or increased
14 Creatinine	Normal or decreased ³¹ 100 3 9
15 Magnesium	Normal serum, but ultrafiltrable fraction is decreased and nonfiltrable (bound) fraction may be normal or increased ⁴⁵ 101
16 Lipids	Decreased (neutral fat normal), no relationship between height of cholesterol and level of neutral fat in serum ⁵ 47 48 55 273
17 Bilirubin	Normal or increased ¹¹ 22 223 301
18 Icteric index	Normal or increased (severe cases) ³⁷ 7
19 Carbon dioxide combining power	Normal ³³ 36 93
20 Amylase	Decreased ³⁵
D FUNCTION TESTS	
1 Tolerance	
a Glucose	
(1) Oral	Normal or decreased (see Table 102) ⁷⁷ 1 3 154 19 257 203 316 387
(2) Intravenous	Decreased (see 103 I J 1 2) ⁷⁷
b Glucose insulin	No data insulin resistance reported ¹³⁴
c Insulin	Diminished (hypoglycemic unresponsiveness)
d Galactose	
(1) Oral	Rarely normal, elevated curve (normal after thyroidectomy) 3 20 23 216 221 226 365 319 314 310
(2) Intravenous	Normal or abnormal ² 20 311
e Iodine (see Chart 139)	Given iodine is removed quickly, no excess present in 6 hrs (average 2%), curve lower than normal ¹⁰ 22-300 373
f Creatine	Marked decrease i.e. 58 per cent (average) retention of amount ingested ¹⁹⁷ 209 306 30 306 329 339 355 358
2 Adrenal water	Normal or positive ³³ 111
3 Salt deprivation	Normal or increased excretion of chlorides ³³ 271
4 Balance	
a Nitrogen	Usually negative but may be normal ²³ 54 ■■ 158 199 19 2 6 not proportionate to level of basal metabolic rate can become positive on high protein intake and after successful therapy ¹⁸⁸
b Calcium	Variable 146 190 31 83 301 negative balance is unrelated to level of basal metabolic rate and may persist after sub total thyroidectomy 145 146 may be related to nitrogen loss which is dependent not only on basal metabolic rate but the ingestion of protein food 294 until nitrogen balance is restored calcium is lost (see 26 XI A 2)
c Phosphorus	Negative or positive (see calcium balance) ¹⁴⁵ 110 254 302
d Potassium	Normal
e Iodine	Negative ⁷⁰ 31
5 Renal	
a Urea clearance	Normal

- 6 Liver Poor efficiency has been demonstrated in severe cases
 a Bromsulfalein Fifty per cent of cases have impaired excretion^{79 72 223 877}
 b Hippuric acid Normal or findings for variable degrees of damage^{23 24}
 32 58 139 173 317 330
 c. Takata ara May be positive⁸
- E MISCELLANEOUS TESTS
- 1 Basal metabolic rate Usually increased rarely normal^{79 8 84 11 12 77}

TABLE 17 RANGE OF METABOLIC RATES AND EFFECT OF IODINE¹⁴³

BMR RANGE (%)	ON ADMISSION		8 TO 10 DAYS LATER	
	No of Cases	Per cent of Total	No of Cases	Per cent of Total
-10 to +20	18	2.9	112	18.5
+21 to +50	212	34.9	363	60.0
+51 or over	377	62.1	132	21.8

Comment. Comparison of basal metabolic rates made on admission and 8 to 10 days later in those having both determinations. It will be noted that 62 per cent of patients had an initial basal metabolic rate of over 50 per cent whereas only 21.8 per cent had similar results 6 to 10 days after receiving iodine in some form.

- 2 Circulation time Decreased (arm to tongue) down to 6 secs, unless congestive heart failure in which case rate may be normal (see Chart 68) increased blood velocity and minute volume⁸³
- 3 Sedimentation rate Normal
- 4 Specific dynamic action of protein Variable²⁰⁰
- 5 Gastric analysis Increased number with achlorhydria^{46 8 84 99 and 203}
 331 39 may be normal or increased (improvement with therapy)^{215 53 239 318}
- 6 Electrocardiogram Variable P and T waves may be high R low 'rolling waves', any change may be present on account of coincidental heart disease (see Table 18)

TABLE 18 ELECTROCARDIOGRAPHIC CHANGES IN HYPERTHYROIDISM*

	PER CENT
Increased height of P waves	7-59
Delayed conduction	3-10
Abnormal T waves	3-22
Low isoelectric or negative T1	1-20
Low isoelectric or negative T2	8-10
High T waves	11-38
Extra systoles	1-14

* Adapted from summary of 22 reports in the literature by Hertz¹³⁸. It is not to be construed that the changes are all due to hyperthyroidism alone but rather to associated cardiovascular disease. The true incidence probably lies between the extremes.

- 7 Blood volume Increased¹⁹
- 8 Spinal fluid proteins Decreased³⁵

■ Fecal excretion	
a Calcium	High ^{14 1 2 51 301}
b Phosphorus	Increased ^{14 301}
c Iodine	Normal or increased ²⁸¹
d Trypsin	Increased ¹⁷
■ Diastase	Increased ¹⁷
10 Electro encephalogram	Alpha rhythm increased ³¹⁰
F URINARY HORMONE ASSAYS	
1 FSH	Negative, may be increased (exclusive of menopausal group) most show 24 ru or less, both males and females ^{11 170 171}
2 LH	No data
3 Estrogens	Normal
4 Pregnandiol	No data
5 17 ketosteroids	Normal or slightly decreased, ^{39 100 11~ 120 122 100 1 328} occasionally may show slight increase ¹⁰⁰ or decrease after iodine therapy ²³
a Androgens (capon test)	Variable ^{10 29}
6 11 oxysteroids	Normal, ³⁰³ decreased ⁹ or increased ^{3 0}
7 Aschheim Zondek	Negative
8 TSH	Decreased or absent (active form) in urine (and blood), increased in the inactive form (see Chart 30) ^{11 71 88 118 10 191 210 290 300 333}
G BIOPSY	
1 Endometrial	Variable
2 Testicular	Normal
H VAGINAL SMEAR	Normal usually
I SEMEN ANALYSIS	Normal probably

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL	
1 Cranial vault	Normal
2 Sella turcica	Normal
3 Mandible	Normal
4 Sinuses	Normal
5 Teeth	Carious frequently
B EPIPHYSEAL STATUS (bone age)	During growth period may show accelerated union of epiphyses ^{44 60 20 377}
C LONG BONES	Increased longitudinal growth if hyperthyroidism occurs during growth period
D VERTEBRAE	Normal ¹⁷⁸ or in longstanding cases osteoporosis occasionally with wedging of vertebrae
E BONE TEXTURE	Normal except cases of long standing show osteoporosis ¹¹
F MISCELLANEOUS	
1 Heart and great vessels (see 30 VIII A)	
a Fluoroscopy	If severe toxicity, forceful and violent heart beats and aortic pulsations, pulmonary arc is straight or convex in 43 per cent ¹⁷⁹ (may be demonstrated by indentation of esophagus on swallowing sugar), limited descent of diaphragm if congestive failure is present

- b Shape (see Fig 196) Cardiac shadow like a ham because of slight auricular enlargement (auricular fibrillation), prominence of ventricles and pulmonary arc dilatation may be present as well as increased hilar shadows in congestive failure
- Cardiac mensuration Size increased frequently,^{1,2} after treatment may decrease or enlarge due to greater body weight i.e. postoperative myxedema or development of heart disease subsequently, superimposition of plates is desirable for comparison due to change in level of diaphragm with congestive failure (lowers it) and weight gain (raises it) (see Chart 45)
- 2 Stomach Normal delay in complete emptying time, increased prominence of gastric rugae, may have duodenal ulcer^{83 151}
- 3 Intestinal tract Increased motility and tone⁶⁴ ■ ■

IX ETIOLOGY

A HYPERSECRETORY HYPERPLASTIC THYROID

1 Unknown primary cause

2 Factors

a Heredity

- (1) Evidence suggests inheritance of a recessive characteristic favorable to its development^{90 233}

- (2) Identical or dissimilar twins may develop hyperthyroidism simultaneously^{5 219 -8}

b Two concepts regarding excess output of thyroid hormone

(1) Driving mechanism'

- (a) The thyroid gland is stimulated by an excess of pituitary thyrotropic hormone which results from some hypothalamic activity forcing unneeded thyroid hormone upon the body

- (b) The inhibiting effect of thyroid hormone is never sufficient to overcome the excess thyrotropic hormone otherwise the disorder would cure itself however this may be one explanation of spontaneous remissions (see 28 II B 3)

- (c) Inadequate iodine intake during stress and strain may contribute to initiating the cycle

- (d) Emotional upheavals influencing brain and hypothalamus due to

(1) Strain (acute or chronic)

- [a] Physical
- [b] Worry
- [c] Grief
- [d] Fear
- [e] Shock

[2] Fever

[3] Starvation

[4] Weight loss in excess¹⁷⁴

[5] Hemorrhage

[6] Thyroid (desiccated) in large amounts¹⁷⁴

- (2) 'Need mechanism'—the body tissues demand greater amounts of thyroid hormone because of a condition induced by primary unknown cause(s)

- (a) Adrenals (alarm reaction of Selye) (see 99)

- (b) Overproduction of pituitary specific metabolic hormone

- (3) The circle of events is the same for both types but the starting point is different

- (4) Hyperthyroidism in an acromegalic patient might be considered as an example of both mechanisms

B HYPERSECRETORY NODULAR GOITER

1 Cause obscure

2 Similar to other hypersecretory tumors

X PATHOLOGY

A Gross

1 Thyroid

- a Symmetrical gland

- (1) Size
 - (a) Normal occasionally
 - (b) Moderately enlarged (50 to 200 Gm)
- (2) Consistency—firm
- (3) Appearance
 - (a) Lobulated
 - (b) Meaty
 - (c) Beefy
- (4) Colloid content poor
- (5) Very vascular
- (6) Cut surface resembles pancreas
- b Nodular type
 - (1) Changes are due to recurring episodes of
 - (a) Hypertrophy
 - (b) Hyperplasia
 - (c) Involution
 - (2) Size and shape of gland and nodules show marked irregularity
 - (3) Consistency
 - (a) Firm
 - (b) Soft
 - (4) Appearance
 - (a) Meaty
 - (b) Translucent
 - (5) Degenerative areas
- 2 Pituitary—normal
- 3 Parathyroids
 - a Normal
 - b Adenoma occasionally found ⁴⁵
- 4 Adrenals^{33 207}
 - a Normal
 - b Atrophy
 - c Hyperplasia
 - d Degenerative changes
- 5 Gonads—normal
- 6 Thymus—present in one half autopsied cases²¹⁵
- 7 Heart
 - a Size may parallel duration and degree of
 - (1) Hyperthyroidism
 - (2) Hypertension
 - (3) Other cardiac disease
 - b Dilatation with¹⁷⁷
 - (1) Auricular fibrillation
 - (2) Congestive heart failure
 - c Hypertrophy may be slight^{61 110 111 176 196 267 307}
 - d Associated pathology from other cardiac disease
 - e The so called brown atrophy has not been reported in recent years¹²⁰
- 8 Liver^{41 66 138 199 214 278 28 311 313 3 37}
 - a General
 - (1) Lesions may be
 - (a) Acute
 - (b) Chronic
 - (c) Combination of both
 - (2) Weight is less than normal in most cases
 - (3) Damaged in 50 per cent of cases
 - (4) Findings depend on the severity and duration of hyperthyroidism
 - b Types of changes
 - (1) Normal
 - (2) Acute degeneration
 - (a) Fatty metamorphosis
 - (b) Necrosis
 - [1] Central
 - [2] Focal
 - (3) Atrophy
 - (a) Simple
 - (b) Subacute
 - (4) Hepatitis (generalized)
 - (5) Cirrhosis²⁰⁰
 - (6) Chronic passive congestion
- 9 Spleen
 - a Normal
 - b Weight increased slightly
 - c Chronic passive congestion
- 10 Kidneys
 - a Normal
 - b Chronic vascular nephritis (associated condition)²¹⁴
- 11 Lymphoid tissue—generalized hyperplasia
- 12 Muscles
 - a Fatty degeneration may be present
 - b Atrophic changes
- 13 Skeleton
 - a Long bones
 - (1) Slender
 - (2) Cortices may be thin
 - b Osteoporosis of variable degrees
- 14 Exophthalmos (if present) (see 33 IV)
- B MICROSCOPIC (see 14 IV B 2 c, d)
 - 1 Thyroid
 - a Before treatment
 - (1) Diffuse hyperplasia
 - (a) Epithelium
 - [1] Columnar
 - [2] Increased size and number of

- [a] Golgi apparatus
- [b] Mitochondria
- [3] Vacuoles increased
- [4] Colloid droplets at apex
- (b) Colloid decreased
- (c) Acini show
 - [1] Increase in size
 - [2] Papillary processes
- (d) Stroma contains
 - [1] Vessels which are
 - [a] Dilated
 - [b] Increased
 - [2] Abundant lymphatic tissue
 - [3] Fibrous tissue (late) which is
 - [a] Dense
 - [b] Thick
- (2) Multiple hypersecretory nodular goiter
 - (a) All types of nodules may be found
 - (b) Adenomas containing the following follicles are the most likely source of hormone
 - [1] Large
 - [2] Small
 - [3] Tubular
 - [4] Papillary
 - (c) Epithelium may be
 - [1] Hypertrophied
 - [2] Hyperplastic
 - (d) Uninvolved tissue may show
 - [1] Involution
 - [2] Colloid nodules
 - [3] Fibrosis
 - [a] Small bands
 - [b] Marked cirrhosis
- (3) Solitary hypersecretory nodule
 - (a) Nodule contains large and small follicular hyperplasia
 - (b) Uninvolved tissue shows involution
- b After treatment (see Figs 197 and 198)
 - (1) Diffuse hyperplasia
 - (a) Iodine—various degrees of involution
 - (b) Thiouracil—increase in hyperplasia
 - (c) Iodine and thiouracil—involution very often
 - (2) Hypersecretory nodules

- (a) Iodine—involution of peripheral cells of adenoma
- (b) Thiouracil—persistence of hyperplasia
- (c) Iodine and thiouracil—no data

2 Pituitary—see 2 IX II 15

XI PATHOLOGIC PHYSIOLOGY

A SUMMARY (see Charts 48 to 50)

- 1 The location of the initial disturbance is unknown
- 2 It may be the result of (see 88 VIII L)
 - a Stimuli from hypothalamus which
 - (1) Originate there
 - (2) Are conveyed from psychic disturbances
 - (3) Increase the amount of thyroid hormone, thus driving the thyroid gland excessively
 - b Some factor which creates a greater demand for thyroid hormone in the tissues thus drawing it out from the thyroid gland or via the pituitary as in the first instance
- 3 Evidence favors an excessive amount of thyroid hormone which causes
 - a Greater metabolic activity in all body cells
 - b Catabolism probably exceeds anabolism with few exceptions i.e. growing child
 - c A loss of
 - (1) Bone calcium
 - (2) Nitrogen
 - (3) Muscle protein
 - (4) Liver glycogen
 - d Depleted state
 - (1) When above processes continue unabated (i.e., excessive combustion) the patient may
 - (a) Literally burn himself up
 - (b) Die in delirium with hyperthermia
 - (2) Under these circumstances
 - (a) Histologic as well as physiologic changes occur in
 - [1] Muscles
 - [2] Liver
 - [3] Other organs
 - (b) Fat stores are used for fuel in an attempt to supply the lost protein
 - (c) Carbohydrate utilization may be inadequate

4 Liver

- a Organic iodine compounds are ⁹¹
 - (1) Broken down
 - (2) Secreted into bile
 - (3) Reabsorbed (partly) by intestines, contributing further to thyroid intoxication
- b Function is reduced especially in severe hyperthyroidism, so that less hormone is destroyed

5 Cardiac changes

- a Histology of cardiac muscle is not characteristically altered ^{91 98 97}
- b The following substances are lost from cardiac muscle ⁹⁵
 - (1) Glycogen
 - (2) Creatine
 - (3) Potassium
 - (4) Phosphate
- c Hypertrophy of only a slight degree is found with coincidental heart disease
- d Dilatation with
 - (1) Auricular fibrillation is frequent with involvement of the auricles
 - (2) Congestive failure is the same as in other cardiac diseases with decompensation without hyperthyroidism (see 27 VII)
- e Auricular fibrillation possibly results from
 - (1) An increase in
 - (a) Thyroid hormone to cardiac muscle
 - (b) Epinephrine secretion ⁹⁰⁷
 - (c) Metabolic rate
 - (2) Auricular dilatation
 - (3) Pre existing heart disease, including degenerative cardiovascular changes
- f No conclusive proof exists that hyperthyroidism
 - (1) Damages the heart although it may produce physiologic exhaustion
 - (2) Associated with auricular fibrillation is evidence of structural abnormalities

6 Adrenals

- a The low excretion of 17 ketosteroids suggests a depression of cortical function although cortin or 11 oxy steroid excretions are not consistently affected ^{92 178 3 0}

b Overactive in some cases possibly ⁹¹

- 7 Lymph glands and thymus may remain undiminished in size, suggesting an inability of the adrenal "S" hormones to operate and instigate the alarm reaction, which might overcome the frequent infections that cause death
- 8 Pulmonary infections are often suspected in thyroid crises but are seldom demonstrated convincingly at postmortem because purulent exudative lesions are not found
- 9 Creatinuria (see Chart 51) ⁹⁵⁰
 - a A result of disturbance in muscle metabolism due to the abnormal liberation of creatine by the thyroid hormone
 - b It is associated with the muscular weakness and apparent dystrophy
 - c Nature of this process is unknown but probably enzymic
- 10 Thyrotropic hormone concentration in
 - a Urine ⁹⁵
 - (1) Active form—decreased
 - (2) Inactive form (reactivated by certain reducing agents)—increased
 - b Blood is decreased because of rapid inactivation by hypersecretory thyroid cells probably ⁹⁵
- 11 Iodine (blood and urine) is increased
 - a Organic or protein bound iodine is the best index of circulating thyroid hormone
 - b The thyroid eventually contains less iodine, and, unless the intake is increased the body loses its reserve
 - c Later, the turnover of iodine becomes more rapid necessitating conservation
 - (1) An enzyme ("iodase" ⁹⁶⁹) capable of more rapid breakdown of organic iodides for absorption and reconversion into thyroid hormone apparently is produced ⁹⁷⁴
 - (2) At such times the blood iodine is reduced to normal levels

XII SYMPTOMATOLOGY

A NEUROMUSCULAR AND SENSORY

- 1 Heat intolerance
- 2 Perspiration excessive usually

- 3 Tremor fine
- 4 Pruritus
- 5 Nervousness
- 6 Emotional instability
- 7 Psychoses
- 8 Insomnia (uncommon)
- 9 Fatigued easily
- 10 Muscular weakness
- 11 Bone pain (rare from osteoporosis³³)
- 12 Coma (infrequent)

B CARDIOVASCULAR

- 1 Tachycardia usually
- 2 Palpitation
- 3 Dyspnea on exertion
- 4 Angina of effort

C GASTROINTESTINAL

- 1 Weight
 - a Loss
 - b Gain by some on account of excess appetite (3.5%)

TABLE 19 WEIGHT CHANGES IN
HYPERTHYROIDISM^{1,3}

POUNDS	NO OF CASES
Weight lost	
1-10	174
11-20	249
21-30	187
31-40	107
41-50	55
51-60	31
61-70	18
Weight gained	28
No change	59
Not recorded	97
Total	1000

- 2 Appetite excellent but anorexia later in disease
 - 3 Thyroid crises (before or during)
 - a Diarrhea
 - b Nausea
 - c Vomiting
- D GENITO URINARY**
- 1 Amenorrhea
 - 2 Oligomenorrhea
 - 3 Frequency due to
 - a Nervousness
 - b Diabetes mellitus
- E MISCELLANEOUS**
- 1 Goiter
 - 2 Exophthalmos
 - a Unilateral
 - b Bilateral

XIII DIAGNOSIS (resume)**A HISTORY**

- 1 Adequate caloric intake with simultaneous weight loss (in absence of diabetes)
- 2 Heat intolerance

B PHYSICAL STATUS

- 1 Skin has greater than normal
 - a Warmth
 - b Moisture
- 2 Eye signs (see 26 VI F 3 b)
 - a Exophthalmos
 - b Stare
 - c Lid retraction
- 3 Thyroid
 - a Visible prominence of gland
 - b Enlarged usually with rare exceptions
 - c Firmer than normal but not always
 - d Bruits in 70 per cent
- 4 Pulse rate and pressure are increased
- 5 Tremor is fine

C LABORATORY DATA

- 1 Cholesterol (plasma) is decreased but not diagnostic
- 2 Iodine (blood and urine) is increased
- 3 Basal metabolic rate may be
 - a Increased in majority
 - b Normal occasionally
- 4 Radioactive iodine—see 14 I\ B 1 ■ and Tables 13 and 24

D COMMENT

- 1 There is no irreducible combination of the above which will invariably establish a diagnosis
- 2 Any one of the above signs or symptoms may be absent
- 3 If the following are all present, the diagnosis seems certain
 - a Weight loss with a proved adequate intake of food in the absence of diabetes mellitus
 - b Basal metabolic rate which is elevated
 - c Exophthalmos (measurable)
- 4 Therapeutic trial of iodine or antithyroid drugs results in
 - a Weight gain
 - b Pulse rate decrease
 - c Basal metabolic rate decline

E NODULAR GOITER WITH HYPERTHYROIDISM (see Fig 194)

- 1 Except in cases of a discrete hypersecretory adenoma,⁷⁶ it is difficult to separate nodular goiter from diffuse hyperplastic goiter on clinical grounds alone
- 2 In the early cases of hypersecretory diffuse hyperplastic goiter, the microscopic picture is characteristic, but in those cases of long standing the differentiation may be extremely difficult
- 3 Hypersecretory diffuse hyperplastic goiter may develop acutely upon a nodular gland, with or without exophthalmos
- 4 The development of hyperplastic goiter may be insidious and the same underlying cause may operate in a person with nodular goiter
- 5 The acute type of hyperthyroidism demands attention because of its severity, whereas the insidious type may exist years before the illness is recognized, causing the hyperplastic gland to become irregularly involuted and nodular

XIV DIFFERENTIAL DIAGNOSIS

A NEUROCIRCULATORY ASTHENIA (including tachycardia, anxiety neurosis and similar conditions)¹⁸⁰

- 1 Anorexia accounts for weight loss, if it has occurred
- 2 Hands are often
 - a Cold
 - b Clammy
- 3 Eyes signs absent
- 4 Goiter
 - a None
 - b Colloid or nodular type may infrequently complicate picture
- 5 Pulse pressure is not increased, except under unusual emotion, especially in potential hypertension
- 6 Quadriceps test negative (see 14 XIII B 5 b)
 - a Patient gives up quickly
 - b No tremor of leg
- 7 Iodine (blood)—normal
- 8 Basal metabolic rate
 - a Normal usually
 - b Several tests may be necessary to establish trend (see 14 XIII D 3)
- 9 No response to Lugol's solution as a therapeutic test

II HYPERTENSION

- 1 Diastolic pressures are higher, except when both diseases coexist
- 2 Weight loss—unusual
- 3 Eyes
 - a Retinal changes more frequent
 - b Exophthalmos may be slight
 - c Other signs absent
- 4 Renal impairment—commoner
- 5 Iodine (blood)—may be elevated
- 6 Basal metabolic rate may be elevated in
 - a A patient with an adrenal medullary tumor
 - b Congestive heart failure
 - c Some cases without either (a b)¹⁸⁰

C DIABETES (see 31, 84 VIII)

- 1 Family history of disease
- 2 Weight loss—common
- 3 Absence of
 - a Heat intolerance
 - b Tremor
 - c Diarrhea
 - d Tachycardia, except with
 - (1) Acidosis
 - (2) Coma
 - e Palpitation
 - f Sweating excessively
- 4 Goiter—absent
- 5 Sugar (blood)—elevated
- 6 Iodine (blood)
 - a Normal
 - b Increased
- 7 Basal metabolic rate
 - a Normal usually
 - b Increased occasionally

D ACROMEGALY

- 1 Headache is very frequent complaint, but rare in hyperthyroidism
- 2 Early in disease there is very little increase (later quite evident) in size of
 - a Facial features
 - b Hands
 - c Feet
- 3 Visual field changes may be found about 20 per cent¹⁷⁸
- 4 Sella turcica is enlarged (over 95%)
- 5 Hyperthyroidism is often an integral part of acromegaly (see 10 V B XVI E 1)

E PULMONARY TUBERCULOSIS

- 1 Anorexia—more common
- 2 Nervousness—less evident
- 3 Fever—usually

- 4 Lesion—may be demonstrated
- 5 Goiter—absent
- 6 Blood studies normal except for
 - a Anemia—secondary
 - b Sedimentation rate—increased
- 7 Basal metabolic rate—normal (in absence of fever or complications)
- 8 It is rarely associated with hyperthyroidism

F MALIGNANCY OF VARIOUS ORGANS

- 1 Progressive weight loss because of decreased caloric intake
- 2 Absence of
 - a Heat intolerance
 - b Nervousness (not marked, if present)
 - c Goiter
- 3 Localization of lesion may be possible
- 4 Iodine (blood)—normal
- 5 Basal metabolic rate
 - a Normal usually
 - b Variable

G AURICULAR FIBRILLATION WITH OR WITHOUT EVIDENT HEART DISEASE

- 1 Hyperthyroidism signs and symptoms are not found
- 2 Goiter absent usually may have non toxic type
- 3 About 6 per cent of all patients with auricular fibrillation have hyperthyroidism but if statistics from large goiter clinics are included, the incidence is 16 per cent (from 4,647 cases collected from the literature by Aastrup¹)

H PARKINSON'S DISEASE

- 1 Tremor
 - a Pill roll coarse
 - b Minimal or absent with voluntary movement
 - c Persistence at rest but stops during sleep
 - d Upper extremities commonly involved but entire body may be affected
- 2 Muscle rigidity
 - a Masklike facies
 - b Slow shuffling gait without arms swinging
 - c Festination
- 3 Sialorrhea

I FACTITIOUS HYPERTHYROIDISM (see 34 \I)

- 1 Eye signs—rarely
- 2 Thyroid enlargement—absent
- 3 Iodine (urinary) excretion—in excess

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A COMPLICATIONS AND SEQUELAE

- 1 Acute thyroid crisis or thyroid storm (see 26 \VI \I 1)
- 2 Persistent hyperthyroidism (see 27)
- 3 Recurrent hyperthyroidism (see 28)
- 4 Myxedema (postoperative) (see 26 \VI \I 12 a)
- 5 Postoperative complications (see below)
- 6 Complications of antithyroid drugs (see 26 \VI D 5)
- 7 Acute congestive heart failure with thyroid crisis
- 8 Congestive heart failure without acute cardiovascular symptoms (see 30 \I)
- 9 Exophthalmos (malignant with severe lid involvement) (see 33 \I)
- 10 Malignant degeneration of thyroid gland^{123 24}
- 11 Liver damage²⁵
- 12 Diabetes mellitus
- 13 Muscular dystrophy
- 14 Vitiligo

B ASSOCIATED DISEASES

- 1 Almost any disease may coexist with hyperthyroidism
- 2 Common
 - a Hypertension
 - b Rheumatic heart disease
 - c Diabetes mellitus
- 3 Rare
 - a Acromegaly (see 10 \V B)
 - b Hypoparathyroidism and hyperparathyroidism^{7 143 146}
 - c Addison's disease^{6 50 60 113 127 178}
 - d Eunuchoidism^{16 178}
 - e Pernicious anemia (19%)⁵¹
 - f Thrombocytopenic purpura⁷
 - g Familial periodic paralysis¹⁶⁷
 - h Myasthenia gravis^{31 81 200 240}
 - i Parkinson's disease
 - j Tuberculosis

XVI TREATMENT

A INTRODUCTION

- 1 The choice of treatment for hyperthyroidism is dependent on several factors
 - a Type of goiter
 - b Severity and duration of the disease
 - c Accessibility of a physician
 - d Desire or conviction of the patient or physician as to the necessity for surgery
- 2 Several methods of treatment are commonly used others have been tried with less favorable acceptance, these will be mentioned but not recommended
- 3 The best procedure for the present may be combined preparation with antithyroid drugs and iodine followed by subtotal thyroidectomy
- 4 Diffuse hyperplastic and nodular goiters with hyperthyroidism are discussed together

B LUGOL'S SOLUTION (or capsules *)

- 1 Indications
 - a This method may be advisable in very mild cases with
 - (1) Basal metabolic rates under plus 25 per cent
 - (2) Little weight loss
 - (3) Diffuse hyperplastic goiter
 - b Therapeutic test—symptoms may be relieved, but may return when medication is discontinued
- 2 Dosage, oral—10 minims t.i.d.p.c. in chocolate milk
- 3 Complication—iodism
 - a Symptoms
 - (1) Rash
 - (2) Nose and eyes are watery
 - (3) Fever
 - b Therapy—discontinue medication
 - Substitute
 - (1) Amends solution
 - (2) Diiodotyrosine
- 4 Results
 - Basal metabolic rate may return to normal
 - b All symptoms may be relieved as long as medication is taken
 - c Underlying cause may persist and/or increase so these patients should then be treated with

- (1) Antithyroid drugs first
 - (2) Subtotal thyroidectomy later
- d Refractoriness to iodine may be attributed to
- (1) Previous and recent intake of this drug
 - (2) Sudden exacerbation of disease neutralizing the effects of iodine
 - (3) Failure to take medication
 - (4) Self induced (factitious) hyperthyroidism
 - (5) Unrecognized acromegaly
 - (6) Wrong diagnosis
- ✓ Diiodotyrosine and potassium iodide produce about the same results, although the first of these has been reported to act more quickly.^{1,2}

C IODINE PREPARATION FOLLOWED BY SUBTOTAL THYROIDECTOMY

1 Indications

- a This procedure may still be used safely without antecedent preparation by antithyroid drugs
 - b In view of the possibility of unpredictable severe postoperative reactions, surgery should not be undertaken unless there has been an excellent response with normal pulse and basal metabolic rate
 - c While the danger is remote, there is no point in risking a severe postoperative storm when antithyroid drugs are available
 - d The method is therefore not recommended any longer
- 2 Dosage—is above B 2
 - 3 Results—summary of principal effects noted on return of normal thyroid function
 - a Certain changes develop after any form of therapy which reduces output of thyroid hormone to normal levels except in point of time
 - b If iodine brings basal metabolic rate to normal it will do so within 10 to 14 days whereas, thiouracil preparations require a longer time depending on height of basal metabolic rate
 - c If the basal metabolic rate continues to fall after 10 to 14 days on iodine it may be said that a 'natural re

TABLE 20 SUMMARY OF EFFECTS ON RETURN OF NORMAL THYROID FUNCTION

	7 TO 14 DAYS	90 DAYS
BMR	Normal	Normal
Pulse (unless auricular fibrillation)	Normal	Normal
Weight	Little or no change	15 to 17 lbs average gain
Cholesterol	Slight rise	Return to values present before onset
Blood pressure		
Systolic	Lower	Lower
Diastolic	Higher	Higher
Blood iodine		
Whole blood (total)	Normal (unless on iodine)	Normal
Plasma protein bound	Normal (unless on iodine)	Normal

mission occurs but if it rises, a natural relapse is taking place

- d If the basal metabolic rate is normal before operation as the result of treatment then the usual changes found in 7 to 14 days after surgery have already taken place

- e Hypertension—except for changes as above course unaltered

- f Cardiac effects—see 30 XIV Charts 52 and 53

- g Exophthalmos

- (1) Unless actual measurements are obtained with the exophthalmometer the true incidence of recession of the eyeball cannot be accurately determined

- (2) On appearance alone a decrease in exophthalmos has been variously reported from 25 to 50 per cent

- (3) In 60 cases measured preoperatively and 100 days postoperatively, the following figures were obtained despite the fact that in many instances there was no noticeable improvement in the appearance of the eyes probably due to less lid retraction (see Fig 207 p 494) ¹

- (4) Actual measurements—see Table 21

- D ANTITHYROID DRUGS (see 14 VI G X B 1 d and Charts 54 and 55 for mode of action)

- 1 Indications—hyperthyroidism that is

- a Mild and without a large gland
b Recurrent
c Persistent

TABLE 21 MEASUREMENT OF EXOPHTHALMOS³³⁴

	NO OF CASES	PER CENT
<i>Initial Examination</i>		
Slight degree	26	60
Significant	10	
No change	24	40
<i>After Operation (100 Days Later)</i>		
Decrease		
/ mm or less	14	23.3
/ to 1 mm	4	6.7
Increase		
1 to 2½ mm	31	51.6
2½ mm or more	11	18.3

- 2 Disadvantages

- a Careful regulation of dosage is necessary for prolonged time
- b Partial control of hypersecretory nodular goiter may be serious in
- (1) Older age group
- (2) Psychotic patients
- (3) Associated heart disease
- c Persistence of goiter (cosmetic)
- d Permanent cure is unlikely and not recommended unless surgery is
- (1) Refused
- (2) Inadvisable
- e Remote dangers in nonsurgical treatment of multiple nodular goiters
- (1) Malignant change in less than 2 per cent (see Table 43, p 537) ⁸⁸
- (2) Tracheal deviation and compression may develop

f Histopathologic changes in thyroid gland have been considered as malignant

g Reactions to medication

✓ 3 Dosage (occasionally larger amounts of all preparations may be employed than given below)—administered orally

a Propylthiouracil
0.3 to 0.4 Gm daily
in divided doses
(2 tablets of 50 mg
each taken b i d or
t i d)

b Thiouracil
(1) Initial 0.4 to 0.6 Gm daily
(2) Maintenance 0.1 to 0.2 Gm daily

c Thiobarbital (no longer available)
10 mg 20 30 40
(1) Initial 0.05 Gm (50 mg)
daily
(2) Maintenance 0.0025 Gm (25
mg) daily

d Methylthiouracil
0.3 Gm daily¹⁸ mg 300

✓ e 1 Methyl 2 mercaptoimidazole
0.003 Gm (30 mg)
daily¹⁴

4 Management

a Continue with medication until basal metabolic rate is normal

b Reduce dose 75 per cent to maintain normal state for 6 to 12 months

c Watch for recurrence of hyperthyroidism

- (1) Immediately
- (2) In 3 to 4 weeks
- (3) After 3 months

d Advise patient to note any signs and symptoms listed below

e Check white blood count and differential

- (1) Thiouracil—every 2 weeks
- (2) Propylthiouracil and methylthiouracil—once a month

5 Toxic effects—symptoms, blood changes and physical manifestations (see Charts 56 and 57)¹⁸ mg 10 20 30 40 50 60 70 80 90 100

1 1 120 130 137 165 181 18 10 235 34 39 211 243 244 296 298 303 34 360 365 38 387

a Onset—usually like a mild upper respiratory infection

b General

- (1) Psychosis
- (2) Chilliness
- (3) Fever
- (4) Hyperhidrosis
- (5) Skin changes
 - (a) Urticaria
 - (b) Rash
- (6) Alopecia
- (7) Pruritus
- (8) Lymphadenopathy
- (9) Exophthalmos may increase

c Neuromuscular

- (1) Headache
- (2) Malaise
- (3) Aching joints

d Gastrointestinal

- (1) Anorexia
- (2) Nausea
- (3) Vomiting
- (4) Diarrhea
- (5) Jaundice
- (6) Polydipsia
- (7) Mouth dryness

e Genito urinary—hematuria

f Hematologic

- (1) Leukopenia
- (2) Agranulocytosis
- (3) Thrombocytopenia
- (4) Anemia
- (5) Purpura

6 Treatment of complications

a Antithyroid preparation discontinued

b Penicillin immediately

- (1) Intravenous
- (2) Intramuscular
- (3) Local throat spray

TABLE 22 TOXICITY OF ANTITHYROID DRUGS (LAHEY CLINIC)³⁰

	NO. OF CASES	% OF TOTAL REACTIONS	% OF AGRANULOCYTOSIS
Propylthiouracil	1273	2.3	0.7
Thiouracil	400	10	1.5
Methylthiouracil	99	13	1.0
1 Methyl 2 mercaptoimidazole	50	0	0
Thiobarbital	28	28	7.1

TABLE 20 SUMMARY OF EFFECTS ON RETURN OF NORMAL THYROID FUNCTION

	7 to 14 Days	90 Days
BMR	Normal	Normal
Pulse (unless auricular fibrillation)	Normal	Normal
Weight	Little or no change	15 to 17 lbs average gain
Cholesterol	Slight ↑	Return to values present before onset
Blood pressure		
Systolic	Lower	Lower
Diastolic	Higher	Higher
Blood iodine		
Whole blood (total)	Normal (unless on iodine)	Normal
Plasma protein bound	Normal (unless on iodine)	Normal

mission' occurs but if it rises a natural relapse is taking place

d If the basal metabolic rate is normal before operation as the result of treatment, then the usual changes found in 7 to 14 days after surgery have already taken place

e Hypertension—except for changes as above course unaltered

f Cardiac effects—see 30 \IV Charts 52 and 53

g Exophthalmos

(1) Unless actual measurements are obtained with the exophthalmometer, the true incidence of recession of the eyeball cannot be accurately determined

(2) On appearance alone a decrease in exophthalmos has been variously reported from 25 to 50 per cent

(3) In 60 cases measured preoperatively and 100 days postoperatively, the following figures were obtained despite the fact that in many instances there was no noticeable improvement in the appearance of the eyes probably due to less lid retraction (see Fig 207 p 494)²¹

(4) Actual measurements — see Table 21

D ANTITHYROID DRUGS (see 14 VI G \ B 1 d and Charts 54 and 55 for mode of action)

- 1 Indications—hyperthyroidism that is
 - a Mild and without a large gland
 - b Recurrent
 - c Persistent

TABLE 21 MEASUREMENT OF EXOPHTHALMOS^{33,4}

	NO OF CASES	PER CENT
<i>Initial Examination</i>		
Slight degree	26	
Significant	10	60
No change	24	40
<i>After Operation (100 Days Later)</i>		
Decrease		
1/2 mm or less	14	23.3
1/2 to 1 mm	4	6.7
Increase		
1 to 2 mm	31	51.6
2 1/2 mm or more	11	18.3

2 Disadvantages

- a Careful regulation of dosage is necessary for prolonged time
- b Partial control of hypersecretory nodular goiter may be serious in
 - (1) Older age group
 - (2) Psychotic patients
 - (3) Associated heart disease
- c Persistence of goiter (cosmetic)
- d Permanent cure is unlikely and not recommended unless surgery is
 - (1) Refused
 - (2) Inadvisable
- e Remote dangers in nonsurgical treatment of multiple nodular goiters
 - (1) Malignant change in less than 2 per cent (see Table 43 p 537)²⁵⁸
 - (2) Tracheal deviation and compression may develop

TABLE 23 CHANGES IN BASAL METABOLIC RATE AND PLASMA CHOLESTEROL ON ADMINISTERING THIOURACIL (28 CASES)

	BMR (%)		PLASMA CHOLESTEROL (MG %)	
	Range	Average	Range	Average
Initial	+26 to +95	+56.3	120 to 215	165
Final	+19 to +27	- 4	144 to 404	228

F IODINE AND ANTITHYROID DRUGS TAKEN SIMULTANEOUSLY BEFORE SURGERY

1 Indications

- This method is recommended for severely toxic cases, both agents being administered simultaneously from the beginning.
- Because of the relatively prompt action of iodine as compared with the slow action of antithyroid drug, thyroid crisis may be prevented in some cases before the latter becomes effective.

2 Dosage—as above

3 Results—as above (D 7), but it may take longer to bring basal metabolic rate to normal because of the interference of iodine with the action of antithyroid drugs (see Chart 58)

G ROENTGEN^{103 135 23 18 74 71 323 341}

1 Over thyroid gland

■ Indications

- When surgery is
 - Contraindicated
 - Refused
- If drug therapy is not tolerated
- Persistent hyperthyroidism
- Recurrent cases

b Method¹⁴⁷

- Thyroid gland just covered by a portal so that all portions receive approximately the same amount of rays
- Six treatments are given in each series, usually 3 series or more are necessary
- Factors
 - K.V.P. 200 milliamperes 20 distance 50 cm
 - Daily dose 300 r
- After 2 months this may be repeated if there has not been a complete cessation in the clinical

evidence of hyperthyroidism

c Complications (none serious, unless thyroid crisis ensues before effect of therapy)

- Redness of the skin because more sensitive than normal
- Sore throat
- Tracheitis
- Esophagitis

d Results

- Thyroid gland may decrease in size
- Clinical condition generally satisfactory
- Severe cases have temporary benefit
- Myxedema may be produced only to be followed by return of thyroid activity in some
- Basal metabolic rate may be
 - Normal
 - Decreased

2 Over pituitary^{3,2 3,3}

a Indication—experimental

b Dosage—see 13 IV

c Results

- Pituitary and surrounding tissues might be damaged
- Percentage of cures is low
- Permanent remission reported in approximately one third of 43 patients

H RADIOACTIVE IODINE¹⁰³

1 Formation

a Fourteen radioactive isotopes of iodine are known and 4 have been used biologically

	HALF LIFE
(1) I ¹²⁷	25 min
(2) I ¹³⁰	12.6 hrs
(3) I ¹³¹	13.0 days
(4) I ¹³²	8.0 days

b I¹³¹ is used almost exclusively at present

- Production by bombarding tellurium¹³⁰ with slow neutrons in the chain reacting pile
- Available at approximately \$1.00 per millicurie from the Atomic Energy Commission Clinton Laboratories Oak Ridge Tenn

- Supportive measures
 - (1) Fluids
 - (2) Oxygen if needed
 - (3) Sedation
 - (4) Transfusions if indicated
- d Subsequent therapy—another thiouracil preparation may be used without toxic effects²⁹⁸

7 Results

- Subjective symptoms disappear first
- b Weight increases as basal metabolic rate approaches normal
- c Cardiac changes
 - (1) Dyspnea decreases
 - (2) Tachycardia responds
 - (3) Auricular fibrillation may revert to normal rhythm
 - (4) Congestive failure may improve
- d Exophthalmos is not altered, except very rarely¹⁷⁸
- e Bone marrow remains normal except with³⁰³
 - (1) Leukopenia
 - (2) Agranulocytosis
- f Diabetes may or may not be affected²⁹⁷
- g Urinary excretion
 - (1) Creatine—decreases
 - (2) Creatinine—increases
- h Blood chemical analyses
 - (1) Globulin (serum)—increases
 - (2) Cholesterol (plasma)—increases
 - (3) Iodine (blood)—returns to normal
- i Electrocardiogram may change as in myxedematous patients^{3 9}
- j Final outcome has been^{9 11 1 - 27}

40	4	00	10	106	11	123	14	20	28
201	204	205	206	204	34	344	374	383	384

398 399

 - (1) Variable
 - (2) Difficult to evaluate at present time
- k Patients treated 6 months or more have a remission, in approximately 25 to 50 per cent of cases, for 1 year or more

■ ANTITHYROID DRUGS FOLLOWED BY IODINE AND SURGERY

- 1 Indication—all cases except very severe hyperthyroidism (see below)
- 2 Dosage
 - a Antithyroid drugs

(1) Oral—see above

(2) Duration of therapy

(a) Diffuse hyperplastic gland

[1] Effective dosage—300 mg daily, but may require 400 mg

[2] Therapy continued until basal metabolic rate is normal

[3] Medication stopped when iodine is given (see below)

[4] Response—basal metabolic rate will drop on average of one point (of per cent elevation) per day (BMR plus 40% will require 40 days of treatment)

(b) Nodular gland

[1] Effective dosage—300 mg daily, but may require 400 mg

[2] Medication continued until basal metabolic rate is normal

[3] Operation is then performed

[4] Response—basal metabolic rate will drop average of one point (of per cent elevation) in every 2 days

✓(3) Morphine should be used with caution for these patients are very sensitive to it

✓b Lugol's solution

✓(1) Oral—10 minims tid pc in chocolate milk

✓(2) Time of administration

(a) Begun when basal metabolic rate is nearly normal

(b) Continued for 7 to 10 days before surgery

(3) NOTE—not necessary in nodular goiter but probably advisable

c Subtotal thyroidectomy (see 26 XVI L 2)—anesthetic course is excellent (see Chart 59)

3 Results—essentially as for antithyroid drugs (see Tables 22 and 23, 26 XVI D 7)

TABLE 24 RESULTS OF TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE

AUTHORS	CASES	ISOTOPE	MICROCURIES /1 GM OF THYROID	TOTAL DOSE mc	RESULTS (No Cases)			
					Good	Fair	Poor	Myxedema
Hertz and Roberts ¹⁶³	79	¹³⁰ ¹³¹		0.7- 28	20		9	
Chapman and Evans ⁶⁰	65	¹³⁰ ¹³¹		15 -147	57	8		11
Chapman ⁶⁵	48	¹³¹	140	4 - 14	36	12		
Soley and Miller ³¹⁰	33	¹³¹		0.8- 9.1	25		8	
Williams et al ³⁹⁰	80	¹³¹		8.5	76			4
Werner et al ³⁷⁸	34	¹³¹	75	2.9- 8.6	30			4
Haines and Keating ¹³⁸	55	¹³¹	250	2.6- 20	45	6	4	15
Feitelberg et al ¹¹⁷	290	¹³¹	80	1.7- 11	278		2	13

The physical units of Werner et al do not agree with the other authors as Geiger counters at the College of Physicians and Surgeons were standardized by ionization chamber measurements. Intercomparison of ^{131}I standards by various laboratories in England, United States and Canada verified the accuracy of absolute activity measurements to the order of ± 2 per cent. ■

[c] 'Effective half life'
(amount of iodine
in gland decreases
both by decay and
by excretion)

[2] Determine total urinary
excretion of radioiodine
for first 72 hrs

(d) Desirable to express doses
in terms of equivalent roent
gens [successful dose in
approximately 15,000 to
30,000 e r (equivalent
roentgens)]

[1] Roentgen, as defined by
international agreement,
applies only to λ or
gamma radiation and
cannot be used for radi
ation due to primary
beta particles

[2] Equivalent roentgen
or 'rep' ('roentgen
equivalent physical' of
the Plutonium Project)
so that amount of beta
radiation which, under
equilibrium conditions
releases in 1 Gm of air
(approximately 83 ergs)
or soft tissue (approx
imately 93 ergs) as
much energy as one
roentgen of gamma rays

(e) Known average energy per
disintegration and half life
in days of radioiodine used

(2) Formula^{114 185 31 303}

(a) Determination of thera
peutic dose (in microcuries)

C =

(Microcuries desired per Gm.
of thyroid) $\times 100 \times$ (esti
mated thyroid weight in Gm.)

Per cent of ^{131}I tracer col
lected by thyroid

(b) Determination of equivalent
roentgens ($e = D\beta + D\gamma$)

[1] $D\beta = 88 \bar{E}\beta T C e r$
per microcurie de
stroyed per Gm
T—the half life of the
isotope in days

$\bar{E}\beta$ —the average energy
per disintegrations
of the beta rays
in million electron
volts

C—the known empiric
initial concentra
tion of microcuries
per Gm of esti
mated thyroid tis
sue

[2] $D\gamma = \lambda\gamma Cg$ roentgens

- (3) Ease of administration—given as a colorless and tasteless drink of water (Some samples may contain enough tellurium to produce garlic odor on breath of patient)
- 2 Action—radioiodine¹³¹ disintegrates to inert and harmless xenon each particle emitting a beta particle and two gamma radiations
- a Beta particles have
- (1) Maximal energy of 0.595 Mev (million electron volts)
 - (2) Average energy of 0.205 Mev
- b Gamma rays have a maximal energy of 0.360 Mev
- c Radioiodine acts physiologically and chemically the same as the stable isotope I^{127} except for the radiation effects
- 3 Indications
- a Radioiodine therapy should be limited to older patients until further clinical experience favors or disproves the fear of radiation injury¹⁰⁷
- b Williams lists the following indications in hyperthyroidism¹⁰⁷
- (1) Poor surgical risks
 - (2) Patients who refuse surgery
 - (3) Postoperative recurrence of hyperthyroidism
 - (4) Vocal cord paralysis
 - (5) Sensitivity, refractoriness or lack of co-operation in taking antithyroid drugs
- c Treatment of
- (1) Euthyroid cardiac patients by producing myxedema (experimental)¹⁰⁷
 - (2) Thyroid cancer
- 4 Dosage
- a Factors reducing thyroid uptake of radioiodine
- (1) Previous iodine therapy^{1, 108, 109}
 - (2) Propylthiouracil¹⁰⁴
 - (3) Thiocyanate¹⁰⁰
 - (4) Reduction in the metabolic rate by exposure to warmth¹⁰⁰
 - (5) Desiccated thyroid administration¹⁰⁵
- b Total amount of iodide administered should be less than 2 mg ($\frac{2}{3}$ drop Lugol's solution)
- c Absorption in gastro intestinal tract
- (1) Radioiodine can be detected in human hand within 3 to 6 min¹¹⁰
 - (2) Absorption complete in 3 hrs (food delays absorption)¹¹³
 - (3) Fecal excretion is not more than 3 per cent¹¹³
- d Deposition of radioiodine in thyroid (see Tables 13 and 24)^{141, 144, 108}
- (1) Thyroid can concentrate iodine to 10 000 times the blood level
 - (2) Uptake in
- | | PER CENT OF DOSE |
|--|------------------|
| (a) Normal thyroid | 15-30 |
| (b) Diffuse toxic or nodular goiter with hyperthyroidism | 40-85 |
- e Urinary excretion
- (1) Large part found in 48 hrs
 - (a) Normal 50-75
 - (b) Hyperthyroidism 5-50
 - (2) The amount found within 72 hrs furnishes an accurate index of the percentage of the dose that will be collected by the thyroid
 - (3) Other body tissues probably take up about 10 to 15 per cent of the radioactive iodine
- f Calculation of radiation dosage
- (1) Bases for calculation
 - (a) Known empiric initial concentration of C microcuries per Gm of thyroid tissue (see Table 24)
 - (b) Clinical estimation of the thyroid gland weight
 - (c) Tracer dose I^{131} of 100 to 150 microcuries of carrier free radioiodine
 - [1] Utilizing a Geiger counter in a fixed position over the thyroid gland determine the
 - [a] Fractional uptake of thyroid
 - [b] Accumulation gradient

- a Indication—to reduce nitrogen loss
- b Dosage
 - (1) Oral—50 mg daily
 - (2) Intramuscular—25 mg daily or every other day during preoperative period
- 5 Sedation to relieve
 - a Tension
 - b Restlessness
 - c Insomnia

L SURGICAL

- 1 Historical data
 - a Multiple stage operations (prior to 1912)¹¹³
 - (1) Pole ligation
 - (a) Procedure — one or both superior and/or inferior thyroid arteries are tied in preparation for partial thyroidectomy
 - (b) Results
 - [1] Temporary amelioration
 - [2] No change
 - [3] Exacerbation
 - [4] Thyroid storm
 - [5] Death
 - (2) Partial or hemithyroidectomy (prior to 1912)¹¹⁵
 - (a) Procedure — one half of gland is removed
 - (b) Results
 - [1] No apparent effect (rare)
 - [2] Thyroid storm
 - [3] Complications
 - [a] Tetany
 - [b] Vocal cord paralysis
 - [4] Basal metabolic rate
 - [a] Decreases about 50 per cent (average)
 - [b] Returns to normal (with iodine)
 - [5] Death
 - (3) Subtotal thyroidectomy or a second hemithyroidectomy (about 1912-1930)¹⁷⁸
 - (a) Procedure — almost complete removal of both lobes
 - [1] Return to normal of
 - [a] Weight

- [b] Pulse
- [c] Basal metabolic rate
- [2] Persistence of disease in some
- [3] Postoperative myxedema
 - [a] Temporary
 - [b] Permanent
- [4] Thyroid storm
- [5] Complications
 - [a] Tetany
 - [b] Vocal cord paralysis

- [6] Death
- (4) Radical subtotal thyroidectomy (about 1930-1942)¹⁷⁸
 - (a) Procedure — radical resection of both lobes
 - (b) Results
 - [1] As above
 - [2] Persistent hyperthyroidism practically eliminated
- (5) Thiouracil era
 - (a) Multiple stage operations discarded
 - (b) Postoperative reactions abolished by antithyroid drugs which prevent hypersecretion of unresected thyroid remnants
 - (c) Friability and vascularity produced by antithyroid drugs decreased by additional use of iodine
- (6) Mortality¹¹⁵

	PER CENT
(a) Prior to 1912 (average)	9
(b) Multiple stage operations	2 3
(c) Iodine and fewer surgical procedures (estimate)	1 3
(d) To date	Less than 115
- (7) Persistence of disease¹⁷⁸

	PER CENT
(a) Before 1912 (partial thyroidectomy)	10-90
(b) 1912-1931 (subtotal thyroidectomy)	10
(c) 1930-1942 (radical subtotal thyroidectomy)	Less than 1
(d) To date	Less than 1

(c) K_y is the number of roentgens at 1 cm. distance in air due to complete disintegration of an infiltrated point source of one microcurie

(d) g is a geometric factor depending on the size and the shape of the tissue mass under consideration and on the absorption of gamma rays (g for thyroid is approximately $4 \pi R$)

(e) R = radius of one lobe of thyroid (estimated)

$$^{130}\text{I} \begin{cases} E\beta = 0.270 \text{ Mev} \\ T = 0.525 \text{ days} \\ K_y = 0.237 \end{cases} \quad ^{131}\text{I} \begin{cases} E\beta = 0.205 \text{ Mev} \\ T = 8.0 \text{ days} \\ K_y = 0.735 \end{cases}$$

(3) Maximum tolerance dose without serious after-effects is not yet determined

(4) Single doses of 250 microcuries of ^{131}I have been given without serious toxic effect

(5) Methods of increasing uptake of radioiodine

(a) Thyrotropic hormone injection³⁶

(b) Removal of normal thyroid by

- [1] Surgery
- [2] Roentgen therapy

(c) Antithyroid drug administration and withdrawal a few days before giving radioiodine

(d) Temporary renal block of radioiodine excretion²⁰

5 Clinical response^{30 128 140 142 221 280}

a Temporary exacerbation of thyrotoxicosis and increased basal metabolic rate due to greater release of thyroid hormone by irradiated tissues⁶⁹

(1) This is usually found when ^{130}I is chief source of radiation

(2) Prophylactic ingestion of ordinary iodine in anticipation of this response will effect the radioiodine by

- (a) Increasing its secretion
- (b) Diminishing its therapeutic action²¹⁵

b Basal metabolic rate decreases in from 2 to 6 weeks

c Cholesterol (plasma) increases

d Transient hypothyroidism or myxedema

e Fibrosis of thyroid

PARA-AMINOBENZOIC ACID^{4 131 272 287}

1 Indication—none, discarded now

2 Dosage

a Oral—1 gr q i d

b Parenteral—1 gr 6 times weekly

3 Results

a Weight—increased

b Pulse—decreased

c Cholesterol (plasma)—increased

d Basal metabolic rate—decreased

4 Toxic reactions¹⁵¹

a Bone marrow depressed

b Renal damage

c Liver may show fatty infiltration

ESTROGENS^{73 116 142 190 208 219 273 321 344 347 349}

1 Indication—experimental

2 Dosage (any estrogenic preparation)

a Oral—1 to 4 mg daily

b Parenteral—210,000 to 3,410,000 Iu over 6 to 16 weeks

c Total amounts used and duration of therapy are variable

3 Results (diverse reports)

a Subjective complaints are improved

b No effect on

(1) Exophthalmos

(2) Goiter size

c Cholesterol (plasma) changes are irregular

d Basal metabolic rate may be lowered

GENERAL

1 Diet

a Calories—3,000 daily if possible

b Protein

(1) 100 to 150 Gm. at least daily^{1 4}

(2) Low intake aids iodine therapy

c Intravenous therapy may be necessary for

(1) Nausea

(2) Vomiting

2 Vitamin B complex in sufficient amounts

3 Calcium intake should be adequate although its clinical importance is questionable

4 Testosterone (see 107 VII A)¹²⁰

out acute cardiovascular symptoms—
see 30 XIII C

✓ 4 Exophthalmos

a Complications

- (1) Acute conjunctivitis
- (2) Acute edema
- (3) Optic nerve edema rarely develops
- (4) Lid retraction
- (5) Eyeballs may "fall out"

b Treatment—see 33 XIV

■ Results—see 33 XIV D 1 d

5 Acute infections

a Types—any kind possible

b Treatment—for specific infection

c Results—good in majority

6 Laryngeal and tracheal complications
100

a Causes (some may be present pre operatively)

(1) Edema and/or ecchymosis in tissues of

- (a) Neck
- (b) Larynx
- (c) Trachea

(2) Hemorrhage into the wound

(3) Compression of larynx and trachea from

- (a) Above (1) and (2)
- (b) Thyroiditis
- (c) New growths
- (d) Enlarged thyroid gland

(4) Paralysis of one or both recurrent laryngeal nerves

- (a) Edema
- (b) Surgical trauma
- (c) New growth

(5) Tracheal obstruction from (1) to (4)

(6) Wound infection secondary to

- (a) Tracheotomy
- (b) Opening of pharynx

(7) Respiratory failure from morphine in thiouracil prepared patients

(8) Tetany—see below

b Symptomatology

- (1) Hoarseness
- (2) Dysphonia
- (3) Dyspnea (especially from hemorrhage)
- (4) Stridor (also due to excessive bleeding)

(5) Cough

(6) Dysphagia

c Treatment

(1) Wound hemorrhage

(a) Urgent for symptoms develop quickly

(b) If an emergency

- [1] Wound opened
- [2] Clot evacuated
- [3] Local pressure until bleeding stops
- [4] Tracheotomy may be indicated

(c) Surgery may be necessary if bleeding

- [1] Cannot be stopped
- [2] Occurs into the thoracic region

(2) Of other causes

(a) Air may be kept free of tenacious secretions by

- [1] Expectorants
- [2] Steam inhalations
- [3] Oxygen administration

(b) Tracheotomy may be necessary for relief of obstruction, unless aided by evacuation of clot (see above)

- [1] For temporary help, an intratracheal tube is inserted through the mouth or the nose and past the obstruction in the larynx or trachea providing

[a] Time to arrange for tracheotomy

[b] Means for administration of oxygen or anesthetic

- [2] Tube should be placed below first tracheal ring

(c) Antibiotics may be used to prevent or control infection when tracheotomy is present

(3) Unilateral recurrent nerve paralysis (vocal cord paralysis)

(a) Symptomatology — hoarseness only

(b) Treatment

- [1] None
- [2] Patient must refrain from forcing voice

2 Subtotal thyroidectomy (see Figs 199-202)

- a Intratracheal nitrous oxide oxygen and ether anesthesia
- b Curved collar incision usually 2 cm above clavicles
- c Division of fat and platysma
- d Incision of deep cervical fascia
- e Free each sternocleidomastoid muscle
- f Midline incision through deep fascia from thyroid cartilage to sternal notch
- g High transverse division of sternohyoid and sternothyroid muscles
- h Partial division of omohyoid muscle
- i Elevation of right lateral lobe with medial retraction
- j Division of middle thyroid veins
- k Complete lateral dissection and retraction of carotid sheath and its contents
- l Identification and ligation in continuity of inferior thyroid artery
- m Exposure of recurrent laryngeal nerve over full course in neck
- n Exposure of inferior parathyroid
- o Double ligation and division of superior thyroid artery and vein
- p Identification of superior parathyroid (provisional)
- q Subtotal excision of lateral lobe and total removal of isthmus and pyramidal lobe leaving small remnant
- r Reconstruction of remnant to tracheal fascia
- s Identical steps for subtotal excision of left lobe
- t Reinspection of all anatomy and vessel pedicles
- u Suture of prethyroid muscles and deep cervical fascia
- v Closure of platysma and skin with clips
- w Wound is closed without drains

VI MANAGEMENT OF COMPLICATIONS

1 Acute thyroid crisis or thyroid storm

- a Crisis before or after surgery
 - (1) An urgent situation
 - (2) This should not occur after operation if patient is properly prepared with thiouracil and/or iodine (see Chart 60)

b Precipitating causes²³⁷

- (1) Emotional strain
- (2) Acute infection
- (3) Gradual exacerbation of hyperthyroidism
- (4) Unknown factors
- (5) Subtotal or hemithyroidectomy

c Symptomatology

- (1) Restlessness extreme
- (2) Delirium
- (3) Psychoses
- (4) Hyperpyrexia
- (5) Tachycardia marked
- (6) Auricular fibrillation (see below)
- (7) Anorexia
- (8) Nausea
- (9) Vomiting
- (10) Diarrhea
- (11) Jaundice
 - (a) Occasional case
 - (b) Mild
- (12) Exhaustion eventually
- (13) Coma

d Treatment

- (1) Morphine— $\frac{1}{2}$ to $\frac{1}{4}$ gr hypodermically by the clock to control restlessness
- (2) Fluids
 - (a) Dosage
 - [1] Intravenous—5 per cent glucose in saline 3 000 to 4 000 cc interrupted or continuously
 - [2] If diabetic, add insulin
- (3) Lugol's solution—10 to 30 minims daily mixed with above intravenous fluids
- (4) Oxygen—may be tried but often is not well tolerated
- (5) Penicillin or sulfonamides for prophylactic purposes in adequate 24 hr doses
- (6) Propylthiouracil administration orally as soon as it can be retained in preoperative thyroid crisis
- (7) Exophthalmos—protect conjunctivae by use of ointments (see below)

2 Acute congestive heart failure with thyroid crisis—see 30 VIII B

3 Chronic congestive heart failure with

- [2] Maintenance — reduce dosage later to patient's requirement
- (c) Calcium lactate—6 to 10 Gm daily dissolved in hot water or any palatable hot liquid
- (3) For chronic parathyroid deficiency—see 37 VIII B
- 8 Paroxysmal auricular fibrillation or flutter—see 30 VIII D
- 9 Pulmonary complications
- a Acute upper respiratory infections
- (1) Variable severity
 - (2) Occurrence may precede other lung complications
- b Bronchopneumonia
- (1) Prophylactic measures
 - (2) Steam inhalations as necessary
 - (3) Antibiotic preparations
- c Atelectasis
- (1) Etiology—mucus plug is most common
 - (2) Treatment
 - (a) Frequent turning of patient may prevent this
 - (b) Bronchoscopy
- d Injury to the pleural cupula¹⁴⁰
- 10 Postoperative embolus
- a Pulmonary—practically unknown
- b Arterial—exceedingly rare but has been observed several times in patients with auricular fibrillation with or without rheumatic heart disease
- 11 Injury to esophagus (rare)¹⁵⁴
- 12 Later developments
- a Postoperative myxedema (see 25 XVI, Chart 61)
- (1) Symptoms may be noticed within a month by patient although clinical signs may take longer to appear
 - (2) Following an operation for diffuse hyperplastic hypersecretory goiter, myxedema may not be permanent (1 out of 3)
 - (3) Withholding treatment for myxedema may favor return of thyroid function but may also encourage recurrence of hyperthyroidism
 - (4) Administration of desiccated thyroid one half to 2 gr daily (as needed) relieves signs and symptoms of myxedema
- (5) When tetany is also present, administration of thyroid for myxedema will help to control this
- b Postoperative low basal metabolic rate without myxedema¹⁷⁸
- (1) Occasionally associated with amenorrhea, origin may be in the
 - (a) Pituitary
 - (b) Hypothalamus
 - (2) Low basal metabolic rate may have existed prior to onset of toxic goiter, but there is no way to prove this
 - (3) Desiccated thyroid does not help much
- c Postoperative hypercholesterolemia may¹⁷⁸
- (1) Indicate thyroid deficiency usually
 - (2) Be transient
 - (3) Have existed before onset of hyperthyroidism (see Chart 62)
- d Weight gain in excess
- (1) Unusual
 - (2) Development in formerly obese individuals
 - (3) Greater caloric intake may be explanation
 - (4) Change in habits of eating after thyroidectomy
 - (5) Prescribed rest may be a factor
- e Sensitivity to cold without signs of myxedema possibly in contrast with former heat intolerance¹⁷⁸
- f Falling of hair¹⁷³
- (1) Occurs often and does not mean myxedema
 - (2) May be due to relatively short period of thyroid deficiency
- g Exophthalmos, postoperative persistence, development of, and/or progression (see 33 XIV)
- h Muscular cramps¹⁷⁸
- (1) Common
 - (2) Unexplained and of no importance
 - (3) Not associated with hypocalcemia
 - (4) Tetany however, should be excluded

(c) Prognosis

- [1] Patient should be reassured
- [2] A good speaking voice will be obtained within a few weeks or months in nearly all cases

(4) Bilateral recurrent nerve paralysis

(a) Types

- [1] Temporary
- [2] Permanent

(b) Symptomatology

- [1] Temporary paralysis if the vocal cords do not approximate then aphonia only or if they do

- [a] Dyspnea
- [b] Labored respiration
- [c] Voice may be quite good

[2] Permanent paralysis

- [a] Air hunger with overexertion
- [b] Roaring noises during sleep so much that others cannot sleep in the vicinity
- [c] Inspiratory crow
- [d] Good voice

(c) Treatment of paralysis

- [1] Temporary—relieve obstruction until function returns (tracheotomy)

[2] Permanent

- [a] Prevention of recurrent nerve injury — most important thing

- [b] Tracheotomy tube (Tucker valve tube which permits in halation through tube and exhalation through larynx) for relief of dyspnea patient has a good voice

- [c] Operative procedure — suture of nerve is unsuccessful

(d) Prognosis

- [1] Temporary—good
- [2] Permanent — tragedy when this injury occurs

✓ 7 Acute parathyroid tetany

a Symptomatology

- (1) Carpopedal spasm
- (2) Numbness and tingling of
 - (a) Hands
 - (b) Feet
 - (c) Side of face
 - (d) Lips
- (3) Laryngeal spasm
- (4) Marked depression
- (5) Anxiety
- (6) Generalized convulsions
- (7) Delirium
- (8) Respiratory distress

b Signs

- (1) Chvostek's sign positive and indicative but not pathognomonic
- (2) Trousseau's sign positive

c Treatment

- (1) For acute tetany and immediate results

- (a) Calcium chloride or gluconate

[1] Dosage

- [a] Intravenous—10 to 20 cc of 10 to 20 per cent solution slowly

- [b] Repeat as necessary

- (b) Glucose—50 to 500 cc of 5 to 20 per cent solution intravenously

- (c) Parathyroid extract (parathyroid hormone)—100 to 300 units parenterally repeat in 12 hrs if necessary

- (2) For subsequent control (to be given at onset) any of the following may be used

- (a) Dihydrotachysterol (A T 10)

- [1] Initial — 1 cc tid orally

- [2] Maintenance — reduce later when blood calcium is normal

- (b) Vitamin D

- [1] Initial—50 000 to 100 000 units orally daily

- (b) Three deaths in 1,850 operated cases from 1942 to 1950
- b Life expectancy following surgical treatment
- (1) Exact morbidity not known
 - (2) The life span of thyrocardiacs is less than that of uncomplicated hyperthyroidism (see 30 XIV)
 - (3) Persistence of auricular fibrillation after cure of hyperthyroidism apparently does not shorten life
 - (4) Recurrence or persistence of hyperthyroidism tends to increase morbidity and complications, if further operations on the thyroid are undertaken
- c Results of subtotal thyroidectomy for primary hyperthyroidism—see Tables 26 and 27

TABLE 26 PRETHIOURACIL ERA

Statistics from the Follow up of 1,016 Cases Operated upon Prior to 1927¹⁸

	CASES
Tetany	
Permanent	7
Transient	4
Cord paralysis	
Unilateral	2
Bilateral	1
Permanent auricular fibrillation following operation	33
Myxedema	
Permanent	49
Temporary (requiring temporary treatment)	22
Operative mortality	
All	16 (1.5%)
Cases with auricular fibrillation	5 (8.4%)

TABLE 27 THIOURACIL ERA

Complications of Subtotal Thyroidectomy (1 000 Cases)¹⁸²

	PER CENT
Tetany	
Permanent	1.5
Transient	1.2
Vocal cord paralysis	1.0
Permanent myxedema	4.2
Mortality	0.2

- d Interval results following therapy—see Tables 28 and 29

TABLE 28 TEN TO 20 YEAR RESULTS OF SUBTOTAL THYROIDECTOMY*
Prethiouracil Era¹⁸

NO OF CASES	RESULTS	DESCRIPTION
386	Excellent	No complaints patient in good health
139	Good	Persistent auricular fibrillation persistent hyperthyroidism controlled or myxedema regulated with thyroid all in satisfactory condition
38	Fair	Ambulatory condition fair but may not be entirely due to thyroid condition if present
26	Poor	Usually incapacitated poor health outcome is not always the result of thyroid disease uncontrolled hyperthyroidism included

* General condition of 589 cases of the original 1,016 cases of primary hyperthyroidism contacted for 10 to 20 years after operation. Similar results have been reported by others.³⁶⁵

TABLE 29 RESULTS OF SUBTOTAL THYROIDECTOMY (462 CASES)
Thiouracil Era⁷⁷

	PER CENT
Two year follow up	95
Recurrence	2.2
Reoperation	0.8
Controlled with Lugol's solution	1.0
Roentgen therapy	0.2
Persistence	0

XVIII CAUSES OF DEATH¹⁸

A SUMMARY

- 1 Thyroid crisis (see Fig 205)
- 2 Acute cardiac decompensation
- 3 Hepatic failure
- 4 Bronchopneumonia
- 5 Alarm reaction possibly—thymus and lymph glands are unable to release immune globulins to aid in state of resistance
- 6 Preoperative
 - a Before surgery completed (pre thiouracil era)—5 out of 1,016 cases (prior to 1927)

- 1 Joint stiffness and arthritis^{17a}
 - (1) Hyperthyroidism often hinders up the arthritic patient
 - (2) Relief of hyperthyroidism may be followed by a return of joint symptoms

✓ N POSTOPERATIVE PROGRAM

- 1 Activity should be limited during the first few months with scheduled rest periods
- 2 Wholesome diet
- ✓ 3 Alcoholic beverages and tobacco (harm of latter has not been demonstrated) should be avoided in excess
- 4 Postoperative use of
 - a Iodine
 - (1) Little value
 - (2) Persistent or recurrent hyperthyroidism may be masked
 - (3) Myxedema may be produced
 - ✓ b Desiccated thyroid (U S P)
 - (1) As a routine procedure may have merit⁶¹
 - (2) Dosage— $\frac{1}{2}$ to 1 gr daily
- 5 Periodic checkup—basal metabolic rate desirable especially 3 months after operation
- 6 Digitalis—continued use may be necessary to control the heart rate with persistent auricular fibrillation
- 7 Pregnancy
 - Inadvisable for at least a year after cure
 - b Safe if no recurrence of hyperthyroidism

XVII PROGNOSIS

A UNTREATED

- 1 Disease may rarely be self limited
- 2 Fatal acute thyroid crisis may occur within a relatively short time^{23a}
- 3 Hyperthyroidism may persist for years with exacerbations but complete remissions of long duration are uncommon

B TREATED

- 1 Medical
 - a Iodine
 - (1) Relief of active symptoms in
 - (a) Mild cases
 - (b) Severe cases partially
 - (2) Disease may
 - (a) Become more intense

TABLE 25 DURATION OF HYPERTHYROIDISM BEFORE SURGICAL TREATMENT (1 016 cases treated before 1927)¹⁸³

YEARS	NO OF CASES	YEARS	NO OF CASES
$\frac{1}{4}$	124	4	43
$\frac{1}{2}$	189	5	48
1	252	7	21
2	118	10	38
3	60	Not stated	123

(b) Return when medication is discontinued

b Thiouracil

- (1) Euthyroid state obtainable in most instances
- (2) Duration of remission varies
- (3) Continual administration necessary to ensure remission
- (4) Relapse rate high^{61 286}

c Radioactive iodine—final evaluation has yet to be made

d Roentgen irradiation of thyroid

- (1) Mild cases may have a permanent cure
- (2) Severe hyperthyroid patients
 - (a) Temporary relief
 - (b) Refractory
- (3) Procedure is not used at present except for
 - (a) Recurrence of the disease
 - (b) Persistent cases
- At present thiouracil and iodine are indicated chiefly in preparation of patients for surgery

2 Surgical (see Figs 203 and 204)

a Factors affecting therapy

- (1) Pre antithyroid drug era the outcome was dependent upon
 - (a) Patient's age
 - (b) Duration of disease
 - (c) Severity of disorder
 - (d) Preoperative response to iodine
 - (e) Skill and experience of surgeon
 - (f) Anesthesia
- (2) Thiouracil era
 - (a) Surgical mortality practically eliminated so that most of the above factors are less important

- 28 Bartels E C and Johnson A C The use of iodine containing capsules in primary hyperthyroidism *Lahey Clin Bull* 5 218 220 (Jan) 1950
- 29 Bartels E C and Bell G O Severe primary hyperthyroidism with normal basal metabolic rate *Lahey Clin Bull* 5 70 73 (Jan) 1947
- 30 Bartels E C and Ingham C C Methyl thiouracil an antithyroid agent *Lahey Clin Bull* 11 174 180 (Oct) 1949
- 31 Bartels E C and Kingley J W Hyperthyroidism associated with myasthenia gravis *Lahey Clin Bull* 11 101 108 (Apr) 1949
- 32 Bartels E C and Perkin H J Liver function in hyperthyroidism as determined by hippuric acid test, *New England J Med* 216 1051 1060 (June) 1937
- 33 Bartels E C Stuart C K and Johnson E C The adrenal gland in hyperthyroidism *Tr Am A Study Gouter* 1940 pp 123 146
- 34 Bartlett W Jr Duration of voluntary apnea in thyrotoxicosis *Surg Gynec & Obst* 63 576 582 (Nov) 1936
- 35 Bartlett Willard Variations of blood amylase with thyroid activity *Trans Third Internat Gouter Conf and Am A Study Gouter* 1938 pp 494 499
- 36 — The essential biochemical derangements in hyperthyroidism *Tr Am A Study Gouter* 1941 pp 48 54
- 37 Bassett A M Loons A H and Salter W T Protein bound iodine in blood V Naturally occurring iodine fractions and their chemical behaviour *Am J M Sc* 202 516 527 (Oct) 1941
- 38 Bauer W and Aub J C Studies of calcium and phosphorus metabolism influence of pituitary gland *J Clin Investigation* 20 295 301 (May) 1941
- 39 Baumann E J and Metzger N Colorimetric estimation and fractionation of urinary androgens assays of normal and pathological urines *Endocrinology* 27 664 669 (Oct) 1940
- 40 Beardwood J T Jr and Levinson D C Thiouracil in medical management of hyperthyroidism *Pennsylvania M J* 48 212 217 (Dec) 1944
- 41 Beaver D C and Pemberton J deJ Pathologic anatomy of liver in exophthalmic goiter *Ann Int Med* 11 687 708 (Dec) 1933
- 42 Beierwaltes W H and Sturges C C Remissions in thyrotoxicosis after discontinuing thiouracil *J A M A* 131 735 738 (June) 1946
- 43 — Complications following administration of thiouracil *Am J M Sc* 212 513 522 (Nov) 1946
- 44 Beilby G M and McClintock J C Hyperthyroidism in children *New York State J Med* 37 563 568 (Mar) 1937
- 45 Berman L Human thyrotoxicosis response to para aminobenzoic acid *Proc Soc Exper Biol & Med* 59 70 72 (May) 1945
- 46 Berryhill W R and Williams H A Study of gastric secretion in hyperthyroidism before and after operation *J Clin Investigation* 11 753 760 (July) 1932
- 47 Bing H J and Heckscher H Der Fett Cholesteringehalt des Blutes bei Patienten mit morbus Basedow *Biochem Ztschr* 158 403 416 (Mar) 1925
- 48 Bissell G W Magnesium partition in hyperthyroidism with special reference to effect of thiouracil *Am J M Sc* 210 195 200 (Aug) 1945
- 49 Blumgart H L Freedberg A S and Ruka R Treatment of euthyroid cardiac patients by producing myxedema with radioactive iodine *Proc Soc Exper Biol & Med* 67 110 191 (Feb) 1948
- 50 Boas N F and Ober W H Hereditary exophthalmic goitre—report of eleven cases in one family *J Clin Endocrinol* 6 575 588 (Aug) 1946
- 51 Boenheim F, Schwimmer D and McGavack T H Combination of hyperthyroidism and pernicious anemia report of case with review of literature *Ann Int Med* 23 869 882 (Nov) 1945
- 52 Boothby W M Fundamental classification of disease by basal metabolic rate *J A M A* 76 84 86 (Jan) 1921
- 53 Boothby W M Sandiford I Sandiford W and Slosse J The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects *Ergeb. Physiol* 24 728 756 (May) 1925
- 54 — The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects *Tr A Am Physicians* 40 195 229 (May) 1925
- 55 Bowers J Z Hyperthyroidism occurring at an early age in dissimilar twins *Ann Int Med* 29 935 941 (Nov) 1949
- 56 Boyce F F and McFetridge E M Studies of hepatic function by Quick hippuric acid test thyroid disease *Arch Surg* 37 427 442 (Sept) 1938
- 57 Boyd E M and Connell W F Lipopenia of hyperthyroidism *Quart J Med* 6 231 239 (July) 1937
- 58 Boyd E M Connell W F and Doyle A M Plasma lipids in anxiety states and their comparison with lipopenia of hyperthyroidism *Quart J Med* 8 47 50 (Jan) 1939
- 59 Bram I Exophthalmic goiter in children comments based upon 128 cases in patients of 13 and under *Arch Pediat* 54 419-424 (July) 1937
- 60 Brenner O Addison's disease with atrophy of cortex of suprarenals *Quart J Med* 29 111 144 (Oct) 1928
- 61 — Thyroid gland and heart disease *Brit M J* 2 199 205 (Aug) 1935
- 62 Brown A Influence of hyperthyroidism upon secretion of free hydrochloric acid *Ann Surg* 92 321 330 (Sept) 1930
- 63 Brown R B and Mearns P M Serum proteins before and after operations for hyperthyroidism *Endocrinology* 22 302 306 (May) 1938
- 64 Brown R B Pendergrass E P and Burdick E D Gastrointestinal tract in hyperthyroidism *Surg Gynec & Obst* 73 766 783 (Dec) 1941
- 65 Byrom F R Nature of myxedema *Clin Sc* 1 273 285 (Nov) 1934
- 66 Cameron G R and Karunaratne W A Liver changes in exophthalmic goitre *J Path & Bact* 41 267 282 (Sept) 1935
- 67 Chang H C The blood volume in hyperthyroidism *J Clin Investigation* 10 475 487 (Aug) 1931
- 68 Chapman E M quoted by Means J H Use of radioactive iodine in the diagnosis and

b This can happen now if iodine is not administered simultaneously with antithyroid drugs in severe cases while awaiting for the latter to take effect

TABLE 30 CAUSES OF DEATH IN HYPER THYROID PATIENTS AFTER SURVIVING SUBTOTAL THYROIDECTOMY^{18,2} (10 to 20 Year Follow up of 589 Cases)

	No of Cases
Cardiovascular disease	14
Cancer	5
Pneumonia	3
Old age	2
Diabetic coma	1
Tetany	1
Childbirth	1
Myasthenia gravis	1
Suicide	1
Postoperative deaths from hernia peritonitis etc	4

REFERENCES

1 Aastrup H Prognostudier ved kroniske Hyperthyroider med Henblik paa Elektrocardiogrammetnes prognostiske Betydning (Disp) Copenhagen 1937

2 Althausen T L Lockhart J C and Soley M H New diagnostic test (galactose) for thyroid disease *Am J M Sc* 199 342 351 (Mar) 1940

3 Althausen T L and Weser G K Galactose tolerance in hyperthyroidism *J Clin Investigation* 16 257 259 (Mar) 1937

4 Anderson I A and Lyall A Addison's disease due to suprarenal atrophy with previous thyrotoxicosis and death from hypoglycaemia *Lancet* 1 1039 1043 (May) 1937

5 Aranow H Elliott R H E Franzt V K Melcher G W and Werner S C Thiouracil in treatment of thyrotoxicosis experience of Thyroid Clinic of Columbia Presbyterian Medical Center *Ann Surg* 124 167 179 (Aug) 1946

6 Astwood E B Treatment of hyperthyroidism with thiouracil and thiouracil *JAMA* 122 78 81 (May) 1943

7 — Medical treatment of hyperthyroidism *Bull New England M Center* 6 1 14 (Feb) 1944

8 — Symposium on surgical lesions of thyroid chemotherapy in hyperthyroidism *Surgery* 16 679 687 (Nov) 1944

9 — Chemotherapy of hyperthyroidism Harvey Lect (1944 1945) 40 195 235 1945

10 — Some observations on use of thiobarbital as antithyroid agent in treatment of Graves disease *J Clin Endocrinol* 5 345 352 (Oct) 1945

11 Astwood E B and Vander Laan W P Thiouracil derivatives of greater activity for treatment of hyperthyroidism *J Clin Endocrinol* 5 424-430 (Dec) 1945

12 — Treatment of hyperthyroidism with propylthiouracil *Ann Int Med* 25 813 821 (Nov) 1946

13 Atkinson F H B Exophthalmic goitre in children *Brit J Child Dis* 35 165 174 (July Sept) 1938

14 Aub J C Bauer W Heath C and Ropes M Studies of calcium and phosphorus metabolism effects of thyroid hormone and thyroid disease *J Clin Investigation* 7 97 137 (Apr) 1929

15 Aub J C Bauer W Ropes M and Heath C Relation of thyroid gland to calcium metabolism *Tr A Am Physicians* 42 344 1927

16 Ballinger J The co existence of hyperthyroidism and prepuberal eunuchoidism in a male *J Clin Endocrinol* 7 566 573 (Aug) 1947

17 Babin and Molinas quoted by Bartels Lipo case in hyperthyroidism *Tr Am A Study Goiter* 1941 pp 204 211

18 Barfred A Methyl thiouracil in treatment of thyrotoxicosis *Am J M Sc* 214 349 362 (Oct) 1947

19 Barker P S Bohannan A L and Wilson F N Atrial fibrillation in Graves disease *Am Heart J* 11 121 127 (Oct) 1932

20 Barnes C G and Kung E J Galactose tolerance tests in thyrotoxicosis *Quart J Med* 12 129 139 (Apr) 1943

21 Barr D P Personal communication

22 Barr D P and Shorr E Observations on treatment of Graves disease with thiouracil *Ann Int Med* 23 754 778 (Nov) 1945

23 Bartels E C Serum protein studies in hyperthyroidism *New England J Med* 218 289 294 (Feb) 1938

24 — Liver function in hyperthyroidism as determined by hippuric acid test *Ann Int Med* 12 652 674 (Nov) 1938

25 — Kidney function in hyperthyroidism *New York State J Med* 39 117 120 (Jan) 1939

26 — Use of thiobarbital in treatment of hyperthyroidism *JAMA* 129 932 935 (Dec) 1945

27 — Thiouracil and allied drugs in hyperthyroidism *New England J Med* 238 6 11 (Jan) 1948

- 28 Bartels E C and Johnson, A C The use of iodine containing capsules in primary hyperthyroidism *Lahey Clin Bull* 6 218 220 (Jan) 1950
- 29 Bartels E C and Bell G O Severe primary hyperthyroidism with normal basal metabolic rate *Lahey Clin Bull* 5 70 73 (Jan) 1947
- 30 Bartels E C and Ingham G C Methyl thiouracil an antithyroid agent *Lahey Clin Bull* 11 174 180 (Oct) 1949
- 31 Bartels E C and Kingley J W Hyperthyroidism associated with myasthenia gravis *Lahey Clin Bull* 6 101 108 (Apr) 1949
- 32 Bartels E C and Perkin H J Liver function in hyperthyroidism as determined by hippuric acid test *New England J Med* 216 1051 1060 (June) 1937
- 33 Bartels E C Stuart C K and Johnson E C The adrenal gland in hyperthyroidism *Tr Am A Study Goiter* 1940 pp 123 146
- 34 Bartlett W Jr Duration of voluntary apnea in thyrotoxicosis *Surg Gynec & Obst* 63 576 582 (Nov) 1936
- 35 Bartlett Willard Variations of blood amylase with thyroid activity *Trans Third Internat Goiter Conf and Am A Study Goiter* 1938 pp 494 499
- 36 — The essential biochemical derangements in hyperthyroidism *Tr Am A Study Goiter* 1941 pp 48 54
- 37 Bassett A M Coons A H and Salter W T Protein bound iodine in blood V Naturally occurring iodine fractions and their chemical behaviour *Am J M Sc* 202 516 527 (Oct) 1941
- 38 Bauer W and Aub J C Studies of calcium and phosphorus metabolism influence of pituitary gland *J Clin Investigation* 20 295 301 (May) 1941
- 39 Baumann E J and Metzger N Colorimetric estimation and fractionation of urinary androgens assays of normal and pathological urines *Endocrinology* 27 664 669 (Oct) 1940
- 40 Beardwood J T Jr and Levinson H C Thiouracil in medical management of hyperthyroidism *Pennsylvania M J* 48 212 217 (Dec) 1944
- 41 Beaver D C and Pemberton J deJ Pathologic anatomy of liver in exophthalmic goiter *Ann Int Med* 7 687 708 (Dec) 1933
- 42 Beierwaltes W H and Sturgis C C Remissions in thyrotoxicosis after discontinuing thiouracil *JAMA* 131 735 738 (June) 1946
- 43 — Complications following administration of thiouracil *Am J M Sc* 212 513 522 (Nov) 1946
- 44 Beilby G H and McClintock J C Hyperthyroidism in children *New York State J Med* 37 563 568 (Mar) 1937
- 45 Berman L Human thyrotoxicosis is response to para aminobenzoic acid *Proc Soc Exper Biol & Med* 59 70 72 (May) 1945
- 46 Berrill W R and Williams H A Study of gastric secretion in hyperthyroidism before and after operation *J Clin Investigation* 11 753 760 (July) 1932
- 47 Bing H I and Heckscher H Der Fett Cholesteringehalt des Blutes bei Patienten mit morbus Basedown *Biochem Ztschr* 158 403 416 (Mar) 1925
- 48 Bissell G W Magnesium partition in hyperthyroidism with special reference to effect of thiouracil *Am J M Sc* 210 195 200 (Aug) 1945
- 49 Blumgart H L Freedberg A S and Ruka R Treatment of euthyroid cardiac patients by producing myxedema with radioactive iodine *Proc Soc Exper Biol & Med* 67 170 191 (Feb) 1948
- 50 Boas N F and Ober W B Hereditary exophthalmic goitre—report of eleven cases in one family *J Clin Endocrinol* 6 575 588 (Aug) 1946
- 51 Boenheim F Schwimmer D and McGavack T H Combination of hyperthyroidism and pernicious anemia report of case with review of literature *Ann Int Med* 23 869 889 (Nov) 1945
- 52 Boothby W M Fundamental classification of disease by basal metabolic rate *JAMA* 76 84 86 (Jan) 1921
- 53 Boothby W M Sandiford I Sandiford H and Slosse J The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects *Ergebn Physiol* 24 728 756 (May) 1925
- 54 — The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects *Tr A Am Physicians* 40 195 229 (May) 1925
- 55 Bowers J Z Hyperthyroidism occurring at an early age in dissimilar twins *Ann Int Med* 29 935 941 (Nov) 1949
- 56 Boyce F F and McFetridge E M Studies of hepatic function by Quick hippuric acid test thyroid disease *Arch Surg* 37 427-442 (Sept.) 1938
- 57 Boyd E M and Connell W F Lipopenia of hyperthyroidism *Quart J Med* 6 231 239 (July) 1937
- 58 Boyd E M Connell W F and Doyle A M Plasma lipids in anxiety states and their comparison with lipopenia of hyperthyroidism *Quart J Med* 47 50 (Jan) 1939
- 59 Bram I Exophthalmic goiter in children comments based upon 128 cases in patients of 12 and under *Arch Pediat* 54 419 424 (July) 1937
- 60 Brenner O Addison's disease with atrophy of cortex of suprarenals *Quart J Med* 27 121 144 (Oct) 1928
- 61 — Thyroid gland and heart disease *Brit M J* 2 199 205 (Aug) 1935
- 62 Brown A Influence of hyperthyroidism upon secretion of free hydrochloric acid *Ann Surg* 92 321 330 (Sept) 1930
- 63 Brown R B and McCray P M Serum proteins before and after operations for hyperthyroidism *Endocrinology* 22 30 306 (Mar) 1938
- 64 Brown R B Pendergrass E P and Burdick E H Gastrointestinal tract in hyperthyroidism *Surg Gynec & Obst* 73 766 783 (Dec) 1941
- 65 Byrom F B Nature of myxoedema *Clin Sc* 1 273 285 (Nov) 1934
- 66 Cameron G R and Karunaratne W A Liver changes in exophthalmic goitre *J Path & Bact* 41 267 282 (Sept) 1935
- 67 Chang H C The blood volume in hyperthyroidism *J Clin Investigation* 10 475 487 (Aug) 1931
- 68 Chapman E M quoted by Means J H Use of radioactive iodine in the diagnosis and

- treatment of thyroid disease Bull New York Acad Med 24 273 286 (May) 1948
- 69 Chaplain E M., and Evans R H Treatment of hyperthyroidism with radioactive iodine J.A.M.A. 131 86 91 (May) 1946
 - 70 Cole V V., and Curtis G M Iodine metabolism of adult rat in relation to trauma thyroid activity and diet J Pharmacol & Exper Therap 56 351 358 (Mar) 1936
 - 71 Collip J B Corticotrophic (adrenotropic) thyrotrophic and parathyrotrophic factors J.A.M.A. 115 2073 2079 (Dec) 1940
 - 72 Conklin S H and Shank P J Thrombocytopenia purpura associated with exophthalmic goiter review of available literature and case report Ohio State M J 40 47 48 (Jan) 1944
 - 73 Cookson H Oestrin in toxic goitre Lancet 2 1069 (Oct.) 1936
 - 74 Cope C L Anterior pituitary lobe in Graves disease and in myxoedema Quart J Med 7 151 170 (Jan) 1938
 - 75 Cope O., and Donaldson G A Relation of thyroid and parathyroid glands to calcium and phosphorus metabolism Study of case with coexistent hypoparathyroidism and hyperthyroidism J Clin Investigation 16 329 341 (May) 1937
 - 76 Cope D Rawson R W., and McArthur J W. Hyperfunctioning single adenoma of thyroid Surg Gynec & Obst 44 415-426 (Apr) 1947
 - 77 Crawford T Carbohydrate tolerance in hypothyroidism and hyperthyroidism Arch Dis Childhood 15 184 198 (Sept) 1940
 - 78 Crile G W The Thyroid Gland Clinics of G W Crile and Associates Philadelphia Saunders 1922 p 283
 - 79 — Liver failure as a factor in postoperative delirium in patients with hyperthyroidism Tr Am A Study Group 1940 pp 42-49
 - 80 Crile G W, McCullagh E P and Glasser O Experience with radioactive iodine in the treatment of hyperthyroidism Cleveland Clin Quart 18 1 7 (Jan) 1949
 - 81 Crotti A The Thyroid and Thymus Philadelphia Lea & Febiger 1922 pp 749 752
 - 82 — Ibid pp 783 786
 - 83 Curschmann H Ueber thyreotoxische Magenstörungen München med Wchnschr 75 425 428 (Mar) 1928
 - 84 Curtis G M and Cole V V The blood iodine in thyroid disease Trans Am A Study Goiter 1934 pp 142 153
 - 85 Curtis G M Davis C H and Phillips F J Significance of iodine content of human blood J.A.M.A. 101 901 905 (Sept) 1933
 - 86 Curtis G M and Fertman M B Blood iodine studies analysis of blood iodine in thyroid disease Arch Surg 80 207 213 (Apr) 1945
 - 87 — Blood iodine studies relation of basal metabolic rate to blood iodine in thyroid disease Ann Surg 122 963 972 (Dec) 1945
 - 88 — Blood iodine studies blood iodine in non thyroid disease Arch Surg 54 541 554 (May) 1947
 - 89 Curtis G M and Puppel I H Increased urinary excretion of iodine in hyperthyroidism Arch Int Med 60 495 508 (Sept) 1937
 - 90 Curtis G M and Swenson R E Thiouracil and its allies in the treatment of hyperthyroidism Internat Abstr Surg 86 100 123 (Feb) 1948
 - 91 Danow L T S Man E B Elkinton J R., Peters J P., and Winkler A W Results of prolonged medical treatment of hyperthyroidism with thiouracil Am J M Sc 215 123 129 (Feb) 1948
 - 92 Daughaday W H., Jaffe H and Williams R H Adrenal cortical hormone excretion in endocrine and nonendocrine disease as measured by chemical assay J Clin Endocrinol 8 244 256 (Nov) 1948
 - 93 Davies H W., Meakins, J., and Sands J Influence of circulatory disturbances on gaseous exchange of blood blood gases and circulation rate in hyperthyroidism Heart 11 299 307 (Dec) 1924
 - 94 Davison T C Chronic hyperthyroidism Am J Surg 35 509 511 (Mar) 1937
 - 95 Dechard and Hermann quoted by Hermann G H Synopsis of Diseases of the Heart and Arteries St Louis Mosby 1944 p 175
 - 96 DeCourcy J L and DeCourcy C B Pathology and Surgery of Thyroid Disease Springfield Thomas 1949 p 405
 - 97 Decourt J Le rôle du corps thyroïde dans la régulation de la chlorémie Ann de med 44 133 144 (July) 1938
 - 98 de Robertis E Assay of thyrotrophic hormone J Clin Endocrinol 8 936 966 (Nov) 1948
 - 99 Deusch G Thyroid and motility of intestines Deutsches Arch f klin Med 142 1 31 (Mar) 1973
 - 100 — Schilddrüse und Hamatopoese Zentralbl f inn Med 48 952 (Sept) 1927
 - 101 Dine R F and Lavieta P H Serum magnesium in thyroid disease J Clin Investigation 21 781 786 (Nov) 1942
 - 102 Dodds E C Lawson W and Robertson J D Variations in iodine content of blood in hyperthyroidism and nontoxic goitre Lancet 2 608 611 (Sept) 1932
 - 103 Don C S D X-ray treatment of exophthalmic goitre Brit M J 1 746 748 (Apr) 1934
 - 104 Drennen E Thiouracil in hyperthyroidism J M A Alabama 15 149 151 (Nov) 1945
 - 105 Dunlop D M Treatment of thyrotoxicosis (with thiouracil) Edinburgh M J 33 257 264 (May) 1948
 - 106 Eaton J C Treatment of thyrotoxicosis with thiouracil Lancet 1 171 174 (Feb) 1945
 - 107 Editorial The use of radioactive iodine in thyrotoxicosis J.A.M.A. 131 140 141 (May) 1946
 - 108 Elmer A W Iodine tolerance test for thyroid insufficiency Endocrinology 18 487-496 (July Aug) 1934
 - 109 Engstrom W W and Mason H L Excretion of 17 ketosteroids in patients with hyperthyroidism and myxoedema J Clin Endocrinol 4 517 527 (Nov) 1944
 - 110 Ernestine A C Heart in hyperthyroidism M Clin North America 17 923 937 (Jan) 1934
 - 111 — Heart in hyperthyroidism Internat Clin 4 78 93 (Dec) 1937
 - 112 Escamille R F Diagnostic significance of urinary hormonal assays report of experience with measurements of 17 keto steroids and follicle stimulating hormone in the urine Ann Int Med 30 249 290 (Feb) 1949
 - 113 Etienne H and Richard G Exophthalmic goiter and Addison's disease Rev frse d'endocrinol 4 1 11 (Feb) 1926

- 114 Evans R D Tissue dosage in radioisotope therapy *Am J Roentgenol* 58 754 756 (Dec) 1947
- 115 Falta Wilhelm The Ductless Glandular Diseases Philadelphia Blakiston 1915 p 151
- 116 Farberman A A Effect of estrogenic hormone on hyperthyroidism *J Clin Endocrinol* 4 17 22 (Jan) 1944
- 117 Feitelberg E Kaunitz P S Silver S Simon N Wasserman L R and Yohalem S B Hyperthyroidism *Arch Int Med* 85 471 478 (Mar) 1950
- 118 Fellinger K Klinische und experimentelle Untersuchungen über das Verhalten und die Bedeutung des thyreotropen Hormons im Blute, Wien *Arch f inn Med* 29 375-406 1936
- 119 File J K Diffuse toxic goiter occurring in a pair of identical twins Frank H Lahey Burdette Volume Springfield Thomas 1940 pp 169 173
- 120 Forbes A., Donaldson E C., Reifenstein E C., and Albright F The effect of trauma and disease on the urinary 17 ketosteroid excretion in man, *J Clin Endocrinol* 1 264 288 (Apr) 1947
- 121 Fowler E F and Cole W H Advantages and limitations of thiouracil therapy in thyrotoxicosis *Surg Gynec & Obst* 84 350 354 (Mar) 1947
- 122 Frazer R W Forbes A P Albright F Sulikowitch H and Reifenstein E Colorimetric assay of 17 ketosteroids in urine, survey of use of this test in endocrine investigation diagnosis and therapy *J Clin Endocrinol* 1 234 256 (Mar) 1941
- 123 Furdess G M and Swenson R E Thiouracil and its allies in the treatment of hyperthyroidism *Internat Abstr Surg* 86 105 123 (Feb) 1948
- 124 Gabrilove J L Kert M J and Soffer L J Use of thiouracil in treatment of patients with hyperthyroidism *Ann Int Med* 23 537 558 (Oct) 1945
- 125 Gardner Hill H Brett P C and Smith J F Carbohydrate tolerance in myxoedema *Quart J Med* 18 377 384 (Apr) 1975
- 126 Gargill S L and Leses M F Toxic reactions to thiouracil report of cases with one fatality *JAMA* 127 890 898 (Apr) 1945
- 127 Gitman L Ant M and Jacobi M Combined hyperthyroidism and adrenal cortical insufficiency effect of iodine therapy case report *Ann Int Med* 19 50, 514 (Sept) 1943
- 128 Goetsch E A new concept regarding the origin of so called primary carcinoma of the hyperplastic thyroid *Ann Surg* 118 843 858 (Nov) 1943
- 129 Goldman B F Goldman A and Kurczok R Treatment of menopausal hyperthyroidism with estrogenic substance *New York State J Med* 40 1178 1184 (Aug) 1940
- 130 Goodpasture E W Myocardial necrosis in hyperthyroidism *JAMA* 76 1545 (June) 1921
- 131 Goodwin J F Miller H and Wayne E J A comparison of the antithyroid activity of para aminobenzoic acid and thiouracil compounds *Lancet* 2 1211 1213 (Dec) 1949
- 132 Gordon S and Graham R M Clinical hyperthyroidism associated with a normal basal metabolic rate *Tr Am A Study Goster* 1934 pp 192 199
- 133 Grainger A, Gregson D A and Pemberton H S Thiouracil in treatment of thyrotoxicosis *Brit M J* 2 343 345 (Sept) 1945
- 134 Griffiths W J Insulin resistance and diagnosis of thyroid disease *Quart J Med* 8 21-40 (Jan) 1939
- 135 Groover T A, et al Roentgen irradiation in treatment of hyperthyroidism statistical evaluation based on 305 cases *JAMA* 92 1730 1734 (May) 1929
- 136 Haban G Über die Leberveränderungen bei Morbus Basedow mit besonderer Berücksichtigung der Lebercirrhose *Beitr z path Anat u z allg Path* 92 88 100 1933
- 137 Haines S F., and Keating F R Jr Unusual reactions following use of thiouracil *J Lab & Clin Med* 30 354 357 (Apr) 1945
- 138 Haines S F Keating F R., Power M H., Williams M D and Kelsey M P The use of radioiodine in the treatment of exophthalmic goiter *J Clin Endocrinol* 8 813 815 (Oct) 1948
- 139 Haines S F Magath T B., and Power M H Hippuric acid test in hyperthyroidism *Ann Int Med* 14 1225 1232 (Jan) 1941
- 140 Hamilton J G The rates of absorption of radioactive isotopes in normal human subjects, *Am J Physiol* 124 667 678 (Dec) 1938
- 141 — The use of radioactive tracers in biology and medicine *Radiology* 39 541 572 (Nov) 1942
- 142 Hamilton J G and Lawrence J H Recent clinical developments in the therapeutic application of radio phosphorus and radio iodine, *J Clin Investigation* 21 674 (Sept) 1942
- 143 Hamilton J G and Soley M H Studies in iodine metabolism by use of new radioactive isotope of iodine *Am J Physiol* 127 557 572 (Oct) 1939
- 144 Hamilton J G Soley M H and Echors K B Deposition of radioactive iodine in human thyroid tissue *Univ California Publ Pharmacol* 1 339 368 1940
- 145 Hansman F S and Carr Fraser W A Calcium and phosphorus metabolism in diseases of thyroparathyroid apparatus calcium and phosphorus balance following therapeutic irradiation of hyperplastic thyroid gland and in hyperthyroidic patients treated with iodine with statistical analysis *J Clin Investigation* 17 543 554 (Sept) 1938
- 146 Hansman F S and Wilson F H Calcium and phosphorus metabolism in diseases of thyroparathyroid apparatus calcium phosphorus and total metabolism in hyperthyroidism and part played by parathyroid glands, *M J Australia* 1 37 66 (Jan) 1934
- 147 Hare, H F Personal communication
- 148 Harris J H and Rose E Further observations on radiation therapy in hyperthyroidism *Am J Roentgenol* 36 610 614 (Nov) 1936
- 149 Harrop G A Polycythemia *Medicine* 7 291 344 (Aug) 1928
- 150 Hedrich, W Kreatinstoffwechsel bei M Basedow und Hyperthyreosen (Zugleich ein Versuch die strahlen resistenten Fälle zu erkennen nebst einem Beitrage zur Frage Senkungsreaktion und M Basedow) *Deutsches Arch f klin Med* 171 27 35 1931
- 151 Heumann F Über den Einfluss von Histamin

- treatment of thyroid disease *Bull New York Acad Med* 24 273 286 (May) 1948
- 69 Chapman M M and Evans R D Treatment of hyperthyroidism with radioactive iodine *JAMA* 131 86 91 (May) 1946
 - 70 Cole V V and Curtis G M Iodine metabolism of adult rat in relation to trauma thyroid activity and diet *J Pharmacol & Exper Therap* 56 351 358 (Mar) 1936
 - 71 Collip J B Corticotrophic (adrenotropic) thyrotropic and parathyrotropic factors *JAMA* 115 2073 2079 (Dec) 1940
 - 72 Conklin S D, and Shank H J Thrombocytopenia purpura associated with exophthalmic goiter review of available literature and case report *Ohio State M J* 40 47 48 (Jan) 1944
 - 73 Cookson H Oestrin in toxic goitre *Lancet* 2 1069 (Oct) 1936
 - 74 Cope C L Anterior pituitary lobe in Graves disease and in myxoedema *Quart J Med* 7 151 160 (Jan) 1938
 - 75 Cope C and Donaldson W A Relation of thyroid and parathyroid glands to calcium and phosphorus metabolism Study of case with coexistent hypoparathyroidism and hyperthyroidism *J Clin Investigation* 16 329 341 (May) 1937
 - 76 Cope D Rawson R W, and McArthur J W Hyperfunctioning single adenoma of thyroid *Surg Gynec & Obst* 84 415-426 (Apr) 1947
 - 77 Crawford T Carbohydrate tolerance in hyperthyroidism and hyperthyroidism *Arch Dis Childhood* 13 184 198 (Sept) 1940
 - 78 Crile G W The Thyroid Gland *Chirac of G W Crile and Associates Philadelphia Saunders* 1922 p 288
 - 79 — Liver failure as a factor in postoperative delirium in patients with hyperthyroidism *Tr Am A Study Goiter* 1940, pp 41-49
 - 80 Crile G McCullagh E P and Glasser O Experience with radioactive iodine in the treatment of hyperthyroidism *Cleveland Clin Quart* 16 1 7 (Jan) 1949
 - 81 Croitti A The Thyroid and Thymus *Philadelphia Lea & Febiger* 1922 pp 749 752
 - 82 *Ibid* pp 753 786
 - 83 Curschmann H Ueber thyreotoxische Magenstörungen München med Wchnschr 75 425 428 (Mar) 1928
 - 84 Curtis G M and Cole V V The blood iodine in thyroid disease *Trans Am A Study Goiter* 1934 pp 142 153
 - 85 Curtis G M Davis C M and Phillips F J Significance of iodine content of human blood *JAMA* 101 901 905 (Sept) 1933
 - 86 Curtis G M and Fertman M M Blood iodine studies analysis of blood iodine in thyroid disease *Arch Surg* 110 207 213 (Apr) 1945
 - 87 — Blood iodine studies relation of basal metabolic rate to blood iodine in thyroid disease *Ann Surg* 122 963 972 (Dec) 1945
 - 88 — Blood iodine studies blood iodine in non thyroid disease *Arch Surg* 54 541 554 (May) 1947
 - 89 Curtis G M and Puppel I H Increased urinary excretion of iodine in hyperthyroidism *Arch Int Med* 60 498 508 (Sept) 1937
 - 90 Curtis G M and Swenson R E Thiouracil and its allies in the treatment of hyperthyroidism *Internat Abstr Surg* 56 105 123 (Feb) 1948
 - 91 Danowski T S Man E H Elkinton J M Peters J P and Winkler A W Results of prolonged medical treatment of hyperthyroidism with thiouracil *Am J M Sc* 215 123 129 (Feb) 1948
 - 92 Daughaday W H Jaffe H and Williams R H Adrenal cortical hormone excretion in endocrine and nonendocrine disease as measured by chemical assay *J Clin Endocrinol* 8 244 256 (Nov) 1948
 - 93 Davies H W Meakins J, and Sands J Influence of circulatory disturbances on gaseous exchange of blood blood gases and circulation rate in hyperthyroidism *Heart* 11 299 307 (Dec) 1924
 - 94 Davison T C Chronic hyperthyroidism *Am J Surg* 35 509 511 (Mar) 1937
 - 95 Dechard and Hermann quoted by Hermann G M Synopsis of Diseases of the Heart and Arteries St Louis Mosby 1944 p 175
 - 96 DeCoursey J L and DeCoursey C H Pathology and Surgery of Thyroid Disease Springfield Thomas 1949 p 405
 - 97 Decourt J Le rôle du corps thyroïde dans la régulation de la chlorémie *Ann de med* 44 133 144 (July) 1938
 - 98 de Robertis E A say of thyrotropic hormone *J Clin Endocrinol* 8 956 966 (Nov) 1948
 - 99 Deutsch G Thyroid and motility of intestines *Deutsches Arch f klin Med* 142 1 31 (Mar) 1925
 - 100 — Schilddrüse und Hamatopoese *Zentralbl f inn Med* 48 952 (Sept) 1927
 - 101 Dunc R F and Lavietes F H Serum magnesium in thyroid disease *J Clin Investigation* 21 781 786 (Nov) 1942
 - 102 Dods E C Lawson W and Robertson J B Variations in iodine content of blood in hyperthyroidism and nontoxic goitre *Lancet* 2 608 611 (Sept) 1932
 - 103 Don C S D X ray treatment of exophthalmic goitre *Brit M J* 1 746 748 (Apr) 1934
 - 104 Drennen E Thiouracil in hyperthyroidism *J M A Alabama* 15 149 151 (Nov) 1945
 - 105 Dunlop D M Treatment of thyrotoxicosis (with thiouracil) *Edinburgh M J* 55 757 764 (May) 1948
 - 106 Easton J C Treatment of thyrotoxicosis with thiouracil *Lancet* 2 171 174 (Feb) 1945
 - 107 Editorial The use of radioactive iodine in thyrotoxicosis *JAMA* 131 140 141 (May) 1946
 - 108 Elmer A W Iodine tolerance test for thyroid insufficiency *Endocrinology* 18 487 496 (July Aug) 1934
 - 109 Engstrom W W and Mason H L Excretion of 17 ketosteroids in patients with hyperthyroidism and myxedema *J Clin Endocrinol* 4 517 527 (Nov) 1944
 - 110 Ernste A C Heart in hyperthyroidism *M Clin North America* 17 923 937 (Jan) 1934
 - 111 — Heart in hyperthyroidism *Internat Clin* 4 78 93 (Dec) 1937
 - 112 Escamille R F Diagnostic significance of urinary hormonal assays report of experience with measurements of 17 ketosteroids and follicle stimulating hormone in the urine *Ann Int Med* 30 249 290 (Feb) 1949
 - 113 Eusebio G and Richard G Exophthalmic goiter and Addison's disease *Rev frse d'endocrinol* 4 1 11 (Feb) 1926

- 198 Kerr W J, and Rusk G Y Acute yellow atrophy associated with hyperthyroidism *M Clin North America* 6 445 459 (Sept) 1922
- 199 Kinsell L W Hertz E and Reifenstein E C Effect of testosterone compounds upon nitrogen balance and creatine excretion in patients with thyrotoxicosis *J Clin Investigation* 23 880 890 (Nov) 1944
- 200 Kowallus E F Haines S F and Pemberton J deJ Goiter with associated myasthenia gravis report of three cases of exophthalmic goiter and one case of adenomatous goiter with hyperthyroidism *Arch Int Med* 69 41 50 (Jan) 1942
- 201 Lahey F H and Bartels E C Use of thiouracil in patients with hyperthyroidism *Ann Surg* 125 572 581 (May) 1947
- 202 Lahey F H Bartels E C Warren S and Meissner W A Thiouracil—its use in pre-operative treatment of severe hyperthyroidism *Surg Gynec & Obst* 81 425-439 (Oct) 1945
- 203 Lahey F H Hurxthal L M and Driscoll R E Thyrocardiac disease review of 614 cases *Ann Surg* 118 681 693 (Oct) 1943
- 204 Larson R A Keating F R Jr, Peacock W and Rawson R W The effect of thiouracil on the collection of radioactive iodine by the thyroid of the chick *Endocrinology* 36 160 169 (Feb) 1945
- 205 Leblond C P Studies on the metabolism of thyroxine in the body *Ann New York Acad Sc* 50 444 449 (Jan) 1949
- 206 Leblond C P Gross J Peacock W and Evans R D Metabolism of radioiodine in the thyroids of rats exposed to high or low temperatures *Am J Physiol* 140 671 675 (Feb) 1944
- 207 LeCompte P M Width of adrenal cortex in lymphatic leukemia lymphosarcoma and by perthyroidism *J Clin Endocrinol* 9 158 162 (Feb) 1949
- 208 Lederer J Action antithyroïdienne de la foliucine en clinique *Rev belge sc méd* 11 326 332 (Aug Sept) 1939
- 209 Lerman J and Means T H Gastric secretion in exophthalmic goitre and myxoedema *J Clin Investigation* 11 167 182 (Jan) 1932
- 210 Lessem M F and Gargill S L Thiouracil as cause of neutropenia and agranulocytosis *New England J Med* 233 803 811 (Dec) 1945
- 211 Levy M S Power M H and Kepler E J Specificity of the water test as a diagnostic procedure in Addison's disease *J Clin Endocrinol* 6 607 632 (Sept) 1946
- 212 Lewis L A and McCullagh E P Electrophoretic analysis of plasma proteins in hyperthyroidism and hypothyroidism *Am J M Sc* 208 727 735 (Dec) 1944
- 213 Lewis H A Effect of hyperthyroidism upon metabolism of vitamin C *Bull Johns Hopkins Hosp* 31-40 (July) 1938
- 214 Lewis W Hyperthyroidism and associated pathology *Am J M Sc* 181 65 74 (Jan) 1931
- 215 Lewit S G Thyroid and gastric secretion *Ztschr f klin Med* 102 440 453 1925
- 216 Lichtman B S Liver function in hyperthyroidism with special reference to galactose tolerance test *Ann Int Med* 14 1199 1215 (Jan) 1941
- 217 Lowenstein H E Bruger M and Hinton J W Protein bound plasma iodine in patients with thyroid disease correlation with basal heat production *J Clin Endocrinol* 4 268-271 (June) 1944
- 218 Lowenstein H E Bruger M Hinton J W Lough W G and Member S Protein bound plasma iodine in patients with thyroid disease effect of thiouracil *J Clin Endocrinol* 5 181 183 (Apr) 1945
- 219 Lueders C W Laboratory methods in diagnosis of hyperthyroidism *Arch Int Med* 24 432 (Oct) 1919
- 220 MacDonald C B Treatment of Graves disease with pancreatic extract *Brit M J* 2 660-661 (Oct) 1937
- 221 MacLagan N F Galactose tolerance in patients with hyperthyroidism *Proc. Roy Soc. Med* 34 607 606 (July) 1941
- 222 Maddock W G Pedersen S and Coller F L Studies of blood chemistry in thyroid crisis, *JAMA* 109 2130-2135 (Dec) 1937
- 223 — Thyroid crisis its relation to liver function and adrenalin *West J Surg* 44 513 521 (Sept) 1936
- 224 Magnuson P and Sørensen U Treatment of hyperthyroidism with methylthiouracil *Acta med Scandinav* 125 263 282 1946
- 225 Man E B Gildea E F, and Peters J P Serum lipids and proteins in hyperthyroidism, *J Clin Investigation* 19 43 59 (Jan) 1940
- 226 Man E B Smurnov A E Gildea E F and Peters J P Serum iodine fractions in hyperthyroidism *J Clin Investigation* 21 773 780 (Nov) 1942
- 227 Maranon G L inter sexualité unilatérale gauche dans l'espèce humaine *Rev frse d'endocrinol* 10 1 35 (Feb) 1932
- 228 Marine D and Lenhart C H Pathological anatomy of exophthalmic goiter the anatomical and physiological relations of the thyroid gland to the disease the treatment *Arch Int. Med* 8 265 316 1911
- 229 Marine D and Rosen E H Urinary excretion of capon comb growth promoting substances in Graves disease and myxoedema and modifications following iodine and desiccated thyroid therapy *J Mt Sinai Hosp* 8 811-819 (Jan Feb) 1942
- 230 Marnelli L D Foote F W Hill R F and Hooker A F Retention of radioactive iodine in thyroid carcinomas *Am J Roentgenol* 58 17 33 (July) 1947
- 231 Marnelli L D Quimby E H and Hine G J Dosage determinations with radioactive isotopes II Practical considerations in therapy and protection *Am J Roentgenol* 59 250-251 (Feb) 1948
- 232 Martin L Results of x ray therapy in thyrotoxicosis *Quart J Med* 11 1 17 (Jan) 1942
- 233 — Hereditary and familial aspects of exophthalmic goitre and nodular goitre *Quart. J Med* 14 207 219 (Oct) 1945
- 234 Ma on R L Hunt H M and Hurxthal L M Blood cholesterol values in hyperthyroidism and hypothyroidism—their significance *New England J Med* 203 1273 1278 (Dec) 1930
- 235 McArthur J W Rawson R W and Means, J H Idiosyncratic febrile reactions to thiouracil clinical characteristics and possible pharmacologic significance *Ann Int Med* 23 915 923 (Dec) 1945
- 236 McArthur J W Rawson R W Means J H

- auf die Aziditätsverhältnisse des Magens bei hyperthyreotischen Erkrankungen Arch f Verdauungkr 49 244 251 (Apr) 1931
- 152 Hendrick J W Hyperthyroidism with normal basal metabolic rate Tr Am A Study Goiter 1938 pp 518 524
 - 153 Hertz John On Goitre and Allied Diseases Especially Thyrotoxicosis Copenhagen Munksgaard London Oxford 1943 pp 99 100
 - 154 *Ibid* p 156
 - 155 *Ibid* pp 171 181
 - 156 *Ibid* p 201
 - 157 *Ibid* p 277
 - 158 *Ibid* p 281
 - 159 Hertz Saul Radioactive iodine as an indicator in thyroid physiology observations on rabbits and on goitre patients Am J Roentgenol 46 467 468 (Oct) 1941
 - 160 Hertz S and Lerman J Blood picture in exophthalmic goitre and its changes resulting from iodine and operation Study by means of supravital technique J Clin Investigation 11 1179 1196 (Nov) 1932
 - 161 Hertz S and Mainini C G Effect of thyroid hormone on growth in thyrotoxic and myxedematous children and adolescents J Clin Endocrinol 1 518 522 (June) 1941
 - 162 Hertz S and Oatler E G Assay of blood and urine for thyrotropic hormone in thyrotoxicosis and myxedema Endocrinology 20 520 525 (July) 1936
 - 163 Hertz S and Roberts A Radioactive iodine in the study of thyroid physiology VII The use of radioactive iodine therapy in hyperthyroidism J A.M.A. 131 81 86 (May) 1946
 - 164 Hertz S Roberts A Means J H and Evans R D Radioactive iodine as an indicator in thyroid physiology II Iodine collection by normal and hypoplastic thyroids in rabbits Am J Physiol 128 565 566 (Feb) 1940
 - 165 Hertz S Roberts A and Salter W T Radioactive iodine as an indicator in thyroid physiology IV The metabolism of iodine in Graves disease J Clin Investigation 21 25 29 (Jan) 1942
 - 166 Hertzler A E Diseases of Thyroid Gland St Louis Mosby 1922 p 245
 - 167 Hildebrand A G and Kepler E J Familial periodic paralysis associated with exophthalmic goiter J Nerv & Ment Dis 94 713 721 (Dec) 1941
 - 168 Himsworth H P et al Thiouracil in treatment of thyrotoxicosis. Lancet 2 13 14 (July) 1944
 - 169 Hoover W B Personal communication
 - 170 Howell L F The excretion of gonadotropic principle in thyroid disease Tr Am A Study Goiter 1940 pp 157 159
 - 171 Howell L P Drpps D G and Fisher H C Presence of excessive amounts of gonadotropic principle in urine of patients with thyroid disease Am J Obst & Gynec 41 868 873 (May) 1941
 - 172 Hunter D The significance to clinical medicine of studies in calcium and phosphorus metabolism Lancet 1 945 957 (May) 1930
 - 173 Hurxthal L M Blood pressure before and after operation in hyperthyroidism Arch Int Med 47 167 181 (Feb) 1931
 - 174 — Exophthalmic goiter following the use of thyroid extract or diet for reduction of weight S Clin North America 11 441-443 (Apr) 1931
 - 175 — Blood cholesterol in thyroid disease analysis of findings in toxic and nontoxic goiter before treatment Arch Int Med 51 22 32 (Jan) 1933
 - 176 — Blood cholesterol in thyroid disease effect of treatment Arch Int Med 52 86 95 (July) 1933
 - 177 — The thyrocardiac F H Lacey Birthday Volume Springfield Thomas 1940 p 245
 - 178 — Unpublished data
 - 179 Hurxthal L M and Menard O J Changes observed in heart shadow in toxic goiter before and after treatment Ann Int Med 6 1634 1643 (June) 1933
 - 180 Hurxthal L M and Parker A S, Jr Diagnosis of borderline hyperthyroidism S Clin North America 23 767 780 (June) 1943
 - 181 Hurxthal L M., and Perkin H J Fractionation of iodine of blood in thyroid disease J Clin Investigation 11 733 737 (Nov) 1939
 - 182 Hurxthal L M Souders C R DePersio J D and Musulin N Ten to twenty year results following subtotal thyroidectomy for primary hyperthyroidism preliminary report on 1016 patients operated upon before 1927 S Clin North America 25 651 656 (June) 1945
 - 183 — Unpublished data
 - 184 Jackson A H Blood picture in 600 cases of goiter special reference to effect of iodine and thyroidectomy J.A.M.A. 97 1954 1956 (Dec) 1931
 - 185 Janney N W., and Isaacson V I Blood sugar in endocrine diseases Arch Int Med 21 160 (Aug) 1918
 - 186 John H J Hyperthyroidism showing carbohydrate metabolism disturbances 10 years study and follow up of cases J A.M.A. 99 6 0 627 (Aug) 1932
 - 187 — Repeated glucose tolerance tests in hyperthyroidism J Clin Endocrinol 2 264 268 (Apr) 1941
 - 188 Johnston J A and Maroney J W Factors affecting retention of nitrogen and calcium in period of growth effect of thyroid on nitrogen retention Am J Dis Child 58 965 982 (Nov) 1939
 - 189 Joll C A quoted by Hertz J On Goitre and Allied Diseases Copenhagen Munksgaard London Oxford 1943 p 156
 - 190 Jonas V and Markalous H Studium des Follikel hormones bei hyperthyreose Ztschr f Gyn 60 2614 2620 (Oct) 1936
 - 191 Jones M S Study of thyrotropic hormone in clinical states Endocrinology 24 665 671 (May) 1939
 - 192 Jones R M Human sternal bone marrow in hyperthyroid and myxedematous states Am J M Sc 200 211 220 (Aug) 1940
 - 193 Kaess K R Personal communication
 - 194 Kay H D Phosphatase in growth and disease of bone Physiol. Rev 12 384-422 (July) 1932
 - 195 Keating F H Radioactive iodine in the study and treatment of thyroid diseases Postgrad Med 3 410-422 (June) 1943
 - 196 Kepler H J and Barnes A R Congestive heart failure and hypertrophy in hyperthyroidism a clinical and pathological study of 178 fatal cases Am Heart J 8 102 108 (Oct) 1932
 - 197 Kepler H J and Boothby W M Creatinuria in hyperthyroidism Am J M Sc 182 476 483 (Oct) 1931

- gout treated with radioactive iodine *JAMA* 140 1082 1089 (July) 1949
- 281 Puppel I D and Curtis G M Calcium and iodine metabolism in thyroid disease *Arch Int Med* 58 957 977 (Dec) 1936
 - 282 — Iodine balance in nodular goiter *J Clin Investigation* 17 729 737 (Nov) 1938
 - 283 Puppel I D Gross H T McCormick E K and Herdle E Rationale of calcium phosphorus and vitamin D therapy in clinical hyperthyroidism *Surg Gynec & Obst* 81 243 265 (Sept) 1945
 - 284 Putman J I Absolute measurements of activity of beta emitters *Brit J Radiol* 23 46 63 (Jan) 1950
 - 285 Ragins A H Value of Takata and Ara reaction as diagnostic and prognostic aid in cirrhosis of liver *J Lab & Clin Med* 20 902 913 (June) 1935
 - 286 Rake G and McFarchem D Study of heart in hyperthyroidism *Am Heart J* 8 19 23 (Oct) 1932
 - 287 Rapport R L and Curtis G M The clinical significance of the blood iodine *J Clin Endocrinol* 10 735 790 (July) 1950
 - 288 Rawson R, quoted by E C Bartels Thiouracil and allied drugs in hyperthyroidism *New England J Med* 238 6 11 (Jan) 1948
 - 289 Rawson R W Graham R M and Riddell C B Physiological reactions of the thyroid stimulating hormone of the pituitary II Effect of normal and pathological human thyroid tissues on the activity of the thyroid stimulating hormone *Ann Int Med* 19 405-414 (Sept) 1943
 - 290 Rawson R W and McArthur J W Radio iodine its use as a tool in the study of thyroid physiology *J Clin Endocrinol* 7 235 263 (Apr) 1947
 - 291 Rawson R W Sterne G D and Aub J C Physiological reactions of the thyroid stimulating hormone on the pituitary Its inactivation by exposure to thyroid tissue *in vitro* and recovery of activity by exposure to heat *Tr Am A Study Goiter* 1941 159
 - 292 Rawson R W and Starr P Direct measurement of height of thyroid epithelium method of assay of thyrotropic substance clinical application *Arch Int Med* 61 726 738 (May) 1938
 - 293 Regan J F and Walder R M Hyperthyroidism and diabetes *Arch Int Med* 65 1116 1122 (June) 1940
 - 294 Reifstein E C Personal communication
 - 295 Reilly W A Thyrotoxicosis *Am J Dis Child* 60 79 87 (July) 1940
 - 296 Reveno W S Effect of thiouracil on human tissues *J Clin Endocrinol* 5 403-406 (Nov) 1945
 - 297 — Observations on use of thiouracil *Ann Int Med* 25 822 831 (Nov) 1946
 - 298 — Propylthiouracil in thyrotoxicosis *JAMA* 133 1190 1192 (Apr) 1947
 - 299 Richardson H H Relation of thyroid gland to Graves disease *M Clin North America* 18 791 809 (Nov) 1934
 - 300 Richardson H B and Shorr E Creatinine metabolism in atypical Graves disease *Tr A Am Physicians* 50 156 159 1935
 - 301 Robertson J D Calcium and phosphorus excretion in thyrotoxicosis and myxoedema *Lancet* 1 672 675 (June) 1942
 - 302 Robinson A R Thyrotropic and antithyrotropic factors in some types of thyroid disease *M J Australia* 1 349 355 (Mar) 1941
 - 303 Rose E and McConnell J Thiouracil in treatment of thyrotoxicosis clinical experience with 37 cases *Am J M Sc* 208 561 566 (Nov) 1934
 - 304 — Thiouracil in thyrotoxicosis Results of prolonged treatment in 35 cases *Am J M Sc* 213 74 80 (Jan) 1947
 - 305 Roess W C Metabolism of creatine and creatinine *Ann Rev Biochem* 2 187 206 1933
 - 306 *Ibid* 4 243 262 1935
 - 307 Rosenblum H H Hahn R G and Levine S A Epinephrine its effect on cardiac mechanism in experimental hyperthyroidism and hypothyroidism *Arch Int Med* 51 279 289 (Feb) 1933
 - 308 Rosenkrantz J A Bruger M and Lockhart A J Studies on galactose tolerance with special reference to thyroid disease *Am J M Sc* 204 36-41 (July) 1942
 - 309 Rosenkrantz J A and Marshall C Basal metabolic rate in hypertensive vascular disease *Arch Int Med* 60 81 83 (July) 1947
 - 310 Ross D A and Schwab R S The cortical alpha rhythm in thyroid disease *Endocrinology* 25 75 79 (July) 1939
 - 311 Rössle R Über die Veränderungen der Leber bei der Basedow'schen Krankheit und ihre Bedeutung für die Entstehung anderer Organ-sklerosen *Virchow's Arch f path Anat* 291 1 46 (Dec) 1933
 - 312 Roth R Blutuntersuchungen bei Morbus Basedow Deutsche med Wchnschr 36 258 1910
 - 313 Rowe A W Endocrine studies association of hepatic dysfunction with thyroid failure *Endocrinology* 17 1 22 (Jan Feb) 1933
 - 314 Saker W T The metabolic circuit of the thyroid hormone *Ann New York Acad Sc* 50 358 376 (Jan) 1949
 - 315 Salter W T Bassett A M and Sappington T H Protein bound iodine in blood its relation to thyroid function in 100 clinical cases *Am J M Sc* 202 527 542 (Oct) 1941
 - 316 Sanger B J and Hun E J Glucose mobilization rate in hyperthyroidism *Arch Int Med* 30 397 406 (Sept) 1922
 - 317 Schmidt C R Walsh W S and Chesky V E Liver insufficiency in toxic goiter and its treatment *Surg Gynec & Obst* 73 502 515 (Oct) 1941
 - 318 Schnabel T G Endocrines in gastric disease *Pennsylvania M J* 24 229 (Jan) 1921
 - 319 Schneeberg N H Likoff W H and Meranze D H Evaluation of blood test for galactose tolerance in diagnosis of hyperthyroidism *Arch Surg* 46 581 583 (Apr) 1943
 - 320 Schneider E Concerning broadening of indications for operation in exophthalmic goiter through recognition at bedside of secondary thyrogenic injury to liver *Internat Clin* 2 8 98 (June) 1934
 - 321 Schwanke W Basedow'sche Krankheit und rotes Blutbild *Klin Wchnschr* 15 346 348 (Mar) 1936
 - 322 Schwartz A R Exophthalmic goiter in children report of case in 2 year old child and review of literature *Arch Pediat* 62 214 218 (May) 1945
 - 323 Schwarz G Present status of roentgen therapy of hyperthyroidism and related endocrine diseases

- and Cope O Thyrotoxic crisis *JAMA* 134 868 874 (July) 1947
- 237 McCullagh M P and Dunlap J H Blood picture in hyperthyroidism and in hypothyroidism *J Lab & Clin Med* 17 1060 1070 (July) 1932
- 238 McCullagh M P Hibbs R E and Schneider R W Propylthiouracil in the treatment of hyperthyroidism *Am J Med Sc* 214 545 552 (Nov) 1947
- 239 McCullagh E P Ryan F J and Schneider R Propylthiouracil in treatment of hyperthyroidism *Cleveland Clin Quart* 13 232 236 (Oct) 1946
- 240 McEathern D and Parnell J L The relationship of hyperthyroidism to myasthenia gravis *J Clin Endocrinol* 8 842 850 (Oct) 1948
- 241 McGavack T H Gerl A J Morton J H Vogel M and Schwimmer D Observations on 78 thyrotoxic patients treated with the surgical *J Clin Endocrinol* 5 259 277 (July-Aug) 1945
- 242 McGavack T H Kenigberg S Shearman A M and Dreker I J Clinical evaluation for 17 ketosteroids by rapid method *J Clin Endocrinol* 6 617 (July) 1948
- 243 McGavack T H Lombardi A and Schummer D Toxic reactions to thiouracil *Bull New York M Coll Flower & Filth Ave Hosps* 8 111 (Apr-June) 1945
- 244 Means J H The Thyroid and Its Diseases Philadelphia Lippincott 1937 p 42
- 245 *Ibid* p 289
- 246 ——— Diseases of thyroid gland *New England J Med* 221 870 875 (Nov) 1939
- 247 ——— Use of radioactive iodine in the diagnosis and treatment of thyroid disease *Bull New York Acad Med* 24 273 286 (May) 1948
- 248 Means J H and Holmes G W Roentgen-ray treatment of toxic goiter *Arch Int Med* 31 303-341 (Mar) 1933
- 249 Menkin V Relative lymphocytosis in hyperthyroidism *Arch Int Med* 42 419 424 (Sept) 1928
- 250 Miesowicz E Basedow's disease with muscular atrophy and insufficient gastric secretion *Wien klin Wchnsch* 17 1206 1208 1904
- 251 Miller E R Soley M H and Danley M E Preliminary report on the clinical use of radioactive iodine (131I) *Am J Roentgenol* 60 45 50 (July) 1948
- 252 Moll H and Flint E R Depressive influence of sympathetic nerves on gastric acidity *Brit J Surg* 16 283 307 (Oct) 1928
- 253 Moll H and Scott R A Gastric secretion in Graves disease *Lancet* 1 68 69 (Jan) 1927
- 254 Moore F D Toxic manifestations of thiouracil therapy *JAMA* 130 315 347 (Feb) 1946
- 255 Muchotwitz E Pathogenesis of carbosus of liver occurring in patients with diffuse toxic goiter *Arch Int Med* 78 497 530 (Nov) 1946
- 256 Müller F Beiträge zur Kenntnis der Basedowischen Krankheit *Deutsches Arch f klin Med* 51 335 417 1892 1893
- 257 Müller H J The production of mutation *J Hered* 38 259 260 (Sept) 1947
- 258 Neff F C Etophthalmic goiter in identical twin girls *J Pediatr* 1 239 242 (Aug) 1932
- 259 Neilson C H Some points in the treatment of hyperacidity especially with reference to the use of hydrogen dioxide *JAMA* 62 434-436 (Feb) 1914
- 260 Newman W W and Garland L R Non surgical treatment of hyperthyroidism complicating heart disease *Surg Gynec & Ob* 1 67 632 639 (Nov) 1938
- 261 Newman E V Thiouracil and hyperthyroidism *M Clin North America* 29 30 322 (Mar) 1945
- 262 Nicholson H C Cardiac arrhythmias of thyrotoxicosis with special reference to prognosis *St Barth Hosp Rep* 70 129 178 1937
- 263 Nickson J J Dosimetric and protective considerations for radioactive iodine *J Clin Endocrinol* 8 721 731 (Sept) 1948
- 264 Nussey A M Thiouracil in treatment of thyrotoxicosis further experiences *Brit M J* 1 364 366 (Apr) 1946
- 265 Palmer W W The effect of iodine on creatinuria in hyperthyroidism *Proc Soc Exper Biol & Med* 25 229 230 (Dec) 1927
- 266 Palmer W W Carson D A and Sloan L W Influence of iodine on excretion of creatinine in exophthalmic goiter *J Clin Investigation* 6 597 608 (Feb) 1929
- 267 Parkinson J and Cookson H Size and shape of heart in goitre *Quart J Med* 24 499 553 (July) 1931
- 268 Pemberton J de J and Lovelace W R Jr Malignant lesions of thyroid gland *S Clin North America* 21 1037 1052 (Aug) 1941
- 269 Perkin H J An iodine in the blood of patients with clinical hyperthyroidism A preliminary report *Labey Clin Bull* 4 124 126 (Apr) 1945
- 270 Perkin H J Brown B R and Lang J Blood iodine content of normal and thyrotoxic individuals Iodine tolerance test *Canad M A J* 31 365 368 (Oct) 1934
- 271 Perkin H J and Labey F H Level of iodine in blood *Arch Int Med* 63 882 895 (May) 1940
- 272 Perkin H J Labey F H and Cattell R B Blood iodine in relation to thyroid disease basic concept of relation of iodine to thyroid gland iodine tolerance test *New England J Med* 214 45 52 (Jan) 1936
- 273 Peters J P and Man E B Interrelations of serum lipids in patients with thyroid disease *J Clin Investigation* 22 715 720 (Sept) 1943
- 274 Pfahler G E Irradiation treatment of hyperthyroidism *Ann Int Med* 7 868 884 (Jan) 1934
- 275 Planch H H Comparison of effectiveness of radiation therapy and estrogenic substances in management of hyperthyroidism *South M J* 39 794 799 (Oct) 1946
- 276 Plummer W A The blood picture in exophthalmic goiter *Minnesota Med* 2 330 332 (Sept) 1919
- 277 ——— Adenomatous goiter with hyperthyroidism accompanied by unusually low metabolic rate *Proc Staff Meet Mayo Clin* 6 329 331 (June) 1931
- 278 Poate H H G Bartholomew R J and Wilson T E Hippuric acid test in thyrotoxicosis *M J Australia* 1 431 490 (May) 1943
- 279 Popp A Oral use of para amino benzoic acid sodium for hyperthyroidism *Marquette M Rev* 13 23 26 (Nov) 1947
- 280 Prunizmet M Agres C M Bergman H C and Smolin B Problem cases of toxic diffuse

- goiter treated with radioactive iodine *JAMA* 140 1082 1089 (July) 1949
- 281 Puppel I D and Curtis G M Calcium and iodine metabolism in thyroid disease *Arch Int Med* 58 957 977 (Dec) 1936
 - 282 — Iodine balance in nodular goiter *J Clin Investigation* 17 729 737 (Nov.) 1938
 - 283 Puppel I D Gross H T McCormick E K and Herdler E Rationale of calcium phosphorus and vitamin D therapy in clinical hyperthyroidism *Surg Gynec & Obst* 81 243 265 (Sept.) 1945
 - 284 Putman J L Absolute measurements of activity of beta emitters *Brit J Radiol* 23 46 63 (Jan) 1950
 - 285 Ragins A H Value of Takata and Ara reaction as diagnostic and prognostic aid in cirrhosis of liver *J Lab & Clin Med* 20 902 913 (June) 1935
 - 286 Rake G and McEachern D Study of heart in hyperthyroidism *Am Heart J* 8 19 23 (Oct.) 1932
 - 287 Rapport R L and Curtis G M The clinical significance of the blood iodine *J Clin Endocrinol* 10 735 790 (July) 1950
 - 288 Rawson H quoted by E C Bartels Thiouracil and allied drugs in hyperthyroidism *New England J Med* 238 6 11 (Jan) 1948
 - 289 Rawson H W Graham R M., and Riddell C B Physiological reactions of the thyroid stimulating hormone of the pituitary II Effect of normal and pathological human thyroid tissues on the activity of the thyroid stimulating hormone *Ann Int Med* 19 405-414 (Sept.) 1943
 - 290 Rawson R W and McArthur J W Radio iodine its use as a tool in the study of thyroid physiology *J Clin Endocrinol* 7 235 263 (Apr.) 1947
 - 291 Rawson R W Sterne G D and Aub J C Physiological reactions of the thyroid stimulating hormone on the pituitary Its inactivation by exposure to thyroid tissue in vitro and recovery of activity by exposure to heat *Tr Am A Study Goiter* 1941 p 159
 - 292 Rawson R W and Starr P Direct measurement of height of thyroid epithelium method of assay of thyrotropic substance clinical application *Arch Int Med* 61 726 738 (May) 1938
 - 293 Regan J F and Wilder R M Hyperthyroidism and diabetes *Arch Int Med* 65 1116 1122 (June) 1940
 - 294 Reifstein E C Personal communication
 - 295 Reilly W A Thyrotoxicosis *Am J Dis Child* 60 79 87 (July) 1940
 - 296 Reveno W S Effect of thiouracil on human tissues *J Clin Endocrinol* 5 403 406 (Nov.) 1945
 - 297 — Observations on use of thiouracil *Ann Int Med* 25 822 831 (Nov.) 1946
 - 298 — Propylthiouracil in thyrotoxicosis *JAMA* 133 1190 1192 (Apr.) 1947
 - 299 Richardson H B Relation of thyroid gland to Graves disease *M Clin North America* 18 791 809 (Nov.) 1934
 - 300 Richardson H B and Shorr E Creatinine metabolism in atypical Graves disease *Tr A Am Physicians* 50 156 159 1935
 - 301 Robertson J D Calcium and phosphorus excretion in thyrotoxicosis and myxoedema *Lancet* 1 672 675 (June) 1942
 - 302 Robinson A R Thyrotropic and antithyrotropic factors in some types of thyroid disease *M J Australia* 1 349 355 (Mar) 1941
 - 303 Rose E and McConnell J Thiouracil in treatment of thyrotoxicosis clinical experience with 37 cases *Am J M Sc* 208 561 566 (Nov.) 1944
 - 304 — Thiouracil in thyrotoxicosis Results of prolonged treatment in 35 cases *Am J M Sc* 213 74 80 (Jan) 1947
 - 305 Ro e W C Metabolism of creatine and creatinine *Ann Rev Biochem* 2 187 206 1933
 - 306 *Ibid* 4 243 262 1935
 - 307 Rosenblum H H Hahn R G and Levine H A Epinephrine its effect on cardiac mechanism in experimental hyperthyroidism and hypothyroidism *Arch Int Med* 51 279 289 (Feb.) 1933
 - 308 Rosenkrantz J A Brugger M and Lockhart A J Studies on galactose tolerance with special reference to thyroid disease *Am J M Sc* 204 36-41 (July) 1942
 - 309 Rosenkrantz J A and Marshall C Basal metabolic rate in hypertensive vascular disease, *Arch Int Med* 80 81 88 (July) 1947
 - 310 Ross D A and Schwab R S The cortical alpha rhythm in thyroid disease *Endocrinology* 25 75 79 (July) 1939
 - 311 Rossle R Über die Veränderungen der Leber bei der Basedow'schen Krankheit und ihre Bedeutung für die Entstehung anderer Organ-sklerosen *Virchow's Arch f path Anat* 291 1-46 (Dec) 1933
 - 312 Roth R Blutuntersuchungen bei Morbus Basedow *Deutsche med Wchnschr* 36 238 1910
 - 313 Rowe A W Endocrine studies association of hepatic dysfunction with thyroid failure *Endocrinology* 17 1 22 (Jan Feb) 1933
 - 314 Salter W T The metabolic circuit of the thyroid hormone *Ann New York Acad Sc* 50 358 376 (Jan) 1949
 - 315 Salter W T Bassett A M and Sappington T S Protein bound iodine in blood its relation to thyroid function in 100 clinical cases *Am J M Sc* 202 527 542 (Oct.) 1941
 - 316 Sanger B J and Hun F J Glucose mobilization rate in hyperthyroidism *Arch Int Med* 30 397 406 (Sept.) 1922
 - 317 Schmidt C R Walh W S and Chesky V E Liver in efficiency in toxic goiter and its treatment *Surg Gynec & Obst* 73 502 515 (Oct.) 1941
 - 318 Schnabel T G Endocrines in gastric disease *Pennsylvania M J* 24 229 (Jan) 1921
 - 319 Schneeberg N M Likoff W H and Meranze D R Evaluation of blood test for galactose tolerance in diagnosis of hyperthyroidism *Arch Surg* 46 581 588 (Apr.) 1943
 - 320 Schneider E Concerning broadening of indications for operation in exophthalmic goiter through recognition at bedside of secondary thyrogenic injury to liver *Internat Clin* 2 87 98 (June) 1934
 - 321 Schwanke W Basedow'sche Krankheit und rotes Bluthild *Klin Wchnchr* 15 346 348 (Mar) 1936
 - 322 Schwartz A R Exophthalmic goiter in children report of case in 2 year old child and review of literature *Arch Pediat* 62 214 218 (May) 1945
 - 323 Schwarz G Present status of roentgen therapy of hyperthyroidism and related endocrine dis-

- turbances *Am J Roentgenol* 55 337-342 (Mar) 1946
- 324 Sexton D L. Thiouracil clinical evaluation following 2½ years experience *South M J* 39 891-897 (Nov) 1946
- 325 Shaffer J M. Disease of liver in hyperthyroidism *Arch Path* 28 20-30 (Jan) 1940
- 326 Shaffer W A. Excretion of creatinin and creatin in health and disease *Am J Physiol* 23 1-22 (Oct) 1908
- 327 Shirer J W. A study of serum protein in hyperthyroidism *Tr Am A Study Gouter* 1932 pp 89-103
- 328 —. Hypermotility of gastrointestinal tract in hyperthyroidism study of 42 cases *Am J M Sc* 186 73-78 (July) 1933
- 329 Shorr E, Richardson H B and Wolff H G. Nature of muscular weakness in Graves disease *J Clin Investigation* 12 966-967 (May) 1933
- 330 —. Endogenous glycine formation in myopathies and Graves disease *Proc Soc Exper Biol & Med* 31 207-209 (Nov) 1933
- 331 Shute W E, and Shute E V. Hyperthyroidism treated by oestrogens *Canad M A J* 46 441-444 (May) 1942
- 332 Sikkema S H, Thewlis E W and Meyer O O. Sternal marrow studies in thyrotoxicosis treated with thiouracil and review of literature regarding thiouracil effects on blood *J Hemat* 1 411-425 (Sept) 1946
- 333 Silver S and Tyson M C. Blood iodine in period after thyroidectomy *J Mt Sinai Hosp* 12 701-707 (May/June) 1945
- 334 Sise H F. Unpublished data
- 335 Skanse B N and Rungs D S. Thyrotoxicosis factitia (alimentary thyrotoxicosis) its differentiation from spontaneous thyrotoxicosis with the aid of radioactive iodine *J Clin Endocrinol* 8 532-543 (July) 1948
- 336 Smith M C, Jondahl W and Ochsner A. Significance of galactose tolerance test in hyperthyroidism *Surg Gynec & Obst* 74 1083-1086 (June) 1942
- 337 Snapper I. Medical Clinics on Bone Diseases ed 2 *New York Interscience* 1949 p 39
- 338 Solfer L J et al. Effect of iodine and adrenalin on thyrotropin in Graves disease and in normal and thyroidectomized dogs *Proc Soc Exper Biol & Med* 64 446-447 (Apr) 1947
- 339 Solval A R, Kung H H and Reimer M. Creatine tolerance test in differential diagnosis of Graves disease and allied conditions *Am J M Sc* 195 608-618 (May) 1938
- 340 Soley M H and Miller E R. Treatment of Graves disease with radioactive iodine *M Clin North America* 32 3-17 (Jan) 1949
- 341 Soley M H and Stane R S. Roentgen ray treatment of hyperthyroidism *Arch Int. Med* 70 1002-1016 (Dec) 1942
- 342 Spence A W. Oestrin in toxic goitre *Lancet* 2 970-974 (Oct) 1936
- 343 Stanley M M. Use of radioactive iodine in study of normal and abnormal thyroid function *Bull New England M Center* 10 28-38 (Feb) 1948
- 344 Stenstrom T. Peroral and intravenous galactose tests comparative study of their significance in different conditions *Acta med Scandinav Suppl* 177 pp 1-115 quoted p 70 1946
- 345 Stenstrom K W and Marvin J F. Urinary excretion of radioactive I^{131} in a case of severe hyperthyroidism *Proc Soc Exper Biol & Med* 66 47-49 (Oct) 1947
- 346 Stokes E H. The Blood Cholesterol Content in Myxedema and other Conditions *Sydney Australia Med Publishing Co* 1941
- 347 Storck A H and Holcombe R G Jr. Use of estrogenic substances in preoperative and postoperative treatment of hyperthyroidism *Surgery* 11 703-709 (May) 1942
- 348 Storck A H and Sabatier J. Use of estrogenic substances in pre and postoperative treatment of hyperthyroidism further observations *Ann Surg* 115 821-828 (May) 1942
- 349 Strauss H. Ueber neurogene und thyrogeene Galaktose *Neurol Centralbl* 32 1281-1284 1913
- 350 Talbot N B. Personal communication
- 351 Thomas H M. Pirmment in the nails during hyperthyroidism *Johns Hopkins Hosp Bull* 52 315-322 (Apr) 1933
- 352 Thompson W O. What's new in endocrinology? *JAMA* 136 314-321 (Jan) 1948
- 353 Thompson W O and Thompson P K. Treatment of toxic goiter by irradiation of pituitary *J Clin Investigation* 23 951 (Nov) 1944
- 354 —. Changes in treatment of toxic goiter produced by thiouracil *J Lab & Clin Med* 30 354 (Apr) 1945
- 355 Thompson W O, Thompson P K, Silveus E and Dailey M E. Protein content of cerebrospinal fluid in myxedema *J Clin Investigation* 6 251-255 (Oct) 1928
- 356 Thorm G W. Creatine studies in thyroid disorders *Endocrinology* 20 678-684 (Sept) 1936
- 357 Thorm G W, quoted by Rawson R W. The Adrenal Thyroid Relationship *Proc of the First Clinical ACTH Conference Philadelphia Blakiston* 1950 p 205
- 358 Thorm G W and Eder H A. Chronic thyrotoxic myopathy *Am J Med* 1 583-601 (Dec) 1946
- 359 Tierney W A and Peters J P. Mode of excretion of creatine and creatinine metabolism in thyroid disease *J Clin Investigation* 22 595-607 (July) 1943
- 360 Trassoff A, Wohl M H and Mintz S S. Fatal agranulocytosis with autopsy following use of thiouracil in case of thyrotoxicosis *Am J M Sc* 211 62-66 (Jan) 1946
- 361 Treusch J V, Kepler E J, Power M H and Haanes S F. Creatinuria in hyperthyroidism and in essential hypertension *Am J M Sc* 208 310-315 (Sept) 1944
- 362 Trunnell J H, Rawson R W, Mannelli L D and Hill R. The effect of thyroid stimulating hormone on the function of human normal and malignant thyroid tissue *J Clin Endocrinol* 8 593 (July) 1948
- 363 Turner K B, DeLamater A and Province, W D. Observations on blood iodine, blood iodine in health in thyroid and cardiorenal disease and in leukemia *J Clin Investigation* 19 515-524 (May) 1940
- 364 Tyrrell E J. Polycythaemia vera (rubra) complicated with hyperthyroidism *Brit M J* 2 596 (Nov) 1919
- 365 Vander Laan W F and Swenson O. Results of surgical treatment in Graves disease *New England J Med* 236 236-238 (Feb) 1947
- 366 Van Winkle W Jr, Hardy E M, Hazel E R, Sharp E A, and Suk W N. Clinical toxicity

- of thiouracil survey of 5745 cases *JAMA* 130 343 347 (Feb.) 1946
- 367 Veil W H and Sturm A Iodine metabolism *Deutsches Arch f klin Med* 147 166 223 (May) 1945
- 368 Venning E H and Browne J S L Excretion of glycogenic corticoids and of 17 keto steroids in various endocrine and other disorders *J Clin Endocrinol* 7 99 101 (Feb) 1947
- 369 Wahlberg J Thyrotoxicosis and action of small doses of iodine on it *Acta med Scand nav Suppl* 14 pp 3 148 1926
- 370 Waller R A and Champer, H A Electrocardiographic observations in normal thyrotoxicomized and thiouracil treated rats *Am J M Sc* 210 443 452 (Oct.) 1945
- 371 Wang M Clinical and experimental investigations on creatine metabolism *Acta med Scand nav Suppl* 105 pp 1 338 1939
- 372 Watson E M Iodine tolerance test for investigation of thyroid function *Endocrinology* 20 358 362 (May) 1936
- 373 — Relation of iodine tolerance to thyroid function *Endocrinology* 22 528 537 (May) 1938
- 374 — Thiouracil in control of thyrotoxicosis *J Clin Endocrinol* 5 273 278 (July Aug.) 1945
- 375 Weller C V Hepatic pathology in exophthalmic goiter *Ann Int Med* 7 543 560 (Nov.) 1933
- 376 Weller C V Wanstrom R C Gordon H and Bugher J C Cardiac histopathology in thyroid disease *Am Heart J* 8 8 18 (Oct) 1932
- 377 Welu H Maladie de Basedow chez l'enfant *Tr Third Internat Goiter Conf and Am A Study Goiter*, 1938 pp 101 107
- 378 Werner S C Cunby, E H and Schmidt C The clinical use of radioactive iodine *Bull New York Acad Med* 24 549 560 (Sept) 1948
- 379 — Radioactive iodine I 131 in the treatment of hyperthyroidism *Am J Med* 7 731 740 (Dec) 1949
- 380 Wilkins L W and Fleischmann W Effects of thyroid on creatine metabolism with a discussion of mechanism of storage and excretion of creatine bodies *J Clin Investigation* 25 360 377 (May) 1946
- 381 Wilkinson M A Gastric acidity in thyroid dysfunction *JAMA* 101 2097 2099 (Dec) 1933
- 382 Williams R H Use of thiouracil in treatment of thyrotoxicosis *M Clin North America* 28 1043 1053 (Sept.) 1944
- 383 — Antithyroid drugs with particular reference to thiouracil *Arch Int Med* 74 479 487 (Dec) 1944
- 384 — Thiouracil treatment of thyrotoxicosis results of prolonged treatment *J Clin Endocrinol* 6 1 22 (Jan) 1946
- 385 — Thyroid and adrenal interrelations with special reference to hypothyroidism axillaris in thyrotoxicosis *J Clin Endocrinol* 7 57 57 (Jan) 1947
- 386 Williams R H Asper S P Rogers W F Jr, Myers J D and Lloyd C W Persistence of remissions of thyrotoxicosis after cessation of thiouracil therapy *New England J Med* 236 737 741 (May) 1947
- 387 Williams R H Antithyroid drugs III Comparison of results of newer forms of treatment of thyrotoxicosis *Arch Int Med* 80 51-56 (July) 1947
- 388 Williams R H and Bissell G W Thiouracil in the treatment of thyrotoxicosis *New England J Med* 229 97 108 (July) 1943
- 389 Williams R H Clute H M Anlen T J and Kenney F R Thiouracil treatment of thyrotoxicosis toxic reactions *J Clin Endocrinol* 6 23 51 (Jan) 1946
- 390 Williams R H Jaffe H and Bernstein B Comparisons of the distribution of radioactive iodine in serum and urine in different levels of thyroid function *J Clin Investigation* 28 1222 1227 (Sept) 1949
- 391 Williams R H Jaffe H Tower B T Rogers W F, Jr and Tagnon R Factors influencing the effectiveness of radioiodotherapy *Am J Med* 7 715 730 (Dec) 1949
- 392 Willis F A, Boothby W M and Wilson L B Heart in exophthalmic goiter and adenoma with hyperthyroidism *M Clin North America* 71 189 219 (July) 1923
- 393 Wilson A Thyrotoxicosis treated with thiouracil and methyl thiouracil *Lancet* 1 640-643 (May) 1946
- 394 Winkler A W Riggs D S, Thompson K W and Man F B Serum iodine in hyperthyroidism with particular reference to effects of subtotal thyroidectomy, *J Clin Investigation* 25 404-412 (May) 1946
- 395 Wolfe J M Die sekretorischen Störungen des Magens bei der Basedow'schen Krankheit *Deutsches Arch f klin Med* 107 492-499 1919
- 396 Woodruff P Behaviour of blood platelets in thyrotoxicosis *M J Australia* 2 150-151 (Aug) 1940
- 397 Youmans J H and Warfield L M Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency *Arch Int Med* 37 1 17 (Jan) 1926
- 398 Zimmermann O Zur Klinik des M. Basedow unter besonderer Berücksichtigung des Blutbildes *Wien klin Wchnschr* 46 265 270 (Mar) 1933
- 399 Zondek H Diseases of Endocrine Glands Baltimore Williams & Wilkins 1944 # 143

FIG 183 HYPERSECRETORY HYPERPLASTIC GOITER Diffusely enlarged gland and hyperthyroidism in a child age 3 (Cattell R II Thyroid disorders in childhood New England J Med. 209 867 875)



FIG 184 HYPERSECRETORY HYPERPLASTIC GOITER
AGE

- 5 Height 46 in Height age 7
 6 Picture above Eyes became prominent at the age of $1\frac{1}{2}$ years Goiter noted as well as palpitation sweating and nervousness No weight loss Weight 40 lbs Height age 6 6 years Pulse 130 BMR plus 60% After iodine for 14 days weight 42 lbs pulse 80 and BMR plus 4% Subtotal thyroidectomy Pathologic diagnosis hyperplasia
 7 Weight 50 lbs Height 48 $\frac{3}{4}$ in Height age 8 Pulse 96 BMR minus 20% Eyes unchanged (Cattell R II Thyroid disorders in childhood New England J Med 209 867 875)



FIG 185 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (*Left*) Age 24 Marked exophthalmos and large hyperplastic gland with severe hyperthyroidism Pulse 128 BMR plus 69% Hemithyroid ectomy performed (*Right*) After second stage operation



FIG 186 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Moderate hyperthyroidism and enlarged hyperplastic gland without exophthalmos in a young man



FIG 187 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Moderate hyperthyroidism in an elderly man Stare, probably slight exophthalmos no visible goiter Small hyperplastic and pebbly gland



FIG 188 VITILIGO Age 28 After child birth extensive vitiligo and hyperthyroidism developed Duration 1 year Weight loss of 24 lbs Weight 102 lbs Pulse 110 BMR plus 84% Four years later weight 128 lbs pulse 80 BMR 0% vitiligo increased



FIG 189 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Age 53 female Undermining of nails in hyperthyroidism (top) and improvement after 69 days of thiouracil treatment (bottom)



FIG 190 UNILATERAL EXOPHTHALMOS AND OPHTHALMOPLÉGIA Age 44 Patient unable to raise right eye to look upward Exophthalmos of the affected eye and possibly some of the other although it appeared to be normal Prominence of eye was noted several months before symptoms of hyperthyroidism Before operation weight 117 lbs pulse 96 BMR plus 69% At the time of photograph which was taken 3 months after subtotal thyroidectomy weight 140 lbs plus 72 BMR plus 9%



FIG 191 CORNEAL ULCER IN HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Age 28 Weight 134 lbs Pulse 96 BMR plus 32% One year after subtotal thyroidectomy weight was 152 lbs and BMR minus 5% Conjunctivitis of left eye developed postoperatively and with corneal ulcer Exophthalmos measured 30 mm bilaterally The outer wall of orbit was resected Prominence of eye reduced 7 mm No further contact with patient



FIG 192 UNILATERAL PARALYSIS OF SUPERIOR RECTUS MUSCLE Mild hyperthyroidism with slight exophthalmos and paralysis of superior rectus muscle on right Note position of right eye when looking straight ahead with left eye Unchanged by subtotal thyroidectomy



FIG 193 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left) Exophthalmos with tearing injection of scleras with edema of lids (Right) Improvement after operation

FIG 194 GRAVE'S DISEASE SUPERIMPOSED ON NODULAR GOITER Age 51 Goiter noted 5 years and 3 months before entry Weight 135 lbs Pulse 132 BMR plus 60% Ten days iodination Weight 141 lbs Pulse 92 BMR plus 24% Pathologic report multiple colloid adenomatous goiter with hyperplasia BMR before second hemithyroidectomy 2 months later plus 64% Weight 136 lbs Pulse 130 BMR plus 21% Ten days later with iodine and rest Weight 137 lbs Pulse 104 BMR plus 27% Apparently no iodine taken between operations The effect of iodine and rest was unmistakable the gland was adenomatous



Various Cardiothoracic Ratios in Toxic and Nontoxic Goiter

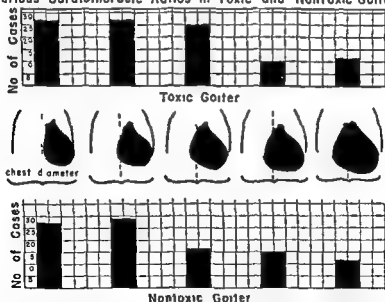


CHART 45 COMPARISON OF INCIDENCE OF VARIOUS CARDIOTHORACIC RATIOS IN 100 CASES OF TOXIC GOITER AND 100 CASES OF NONTOKIC GOITER The similarity is striking The incidence of enlarged hearts in non toxic goiter probably is due to a greater number of cases with cardio vascular disease which were referred on suspicion that goiter might be the cause of hypertension etc This illustrates the difficulty in determining the actual role played by hyperthyroidism on the heart when the latter is found to be enlarged in toxic goiter (Hurthall L M and Menard O J Changes observed in the heart shadow in toxic goiter before and after treatment Ann Int Med. 1634-1643)

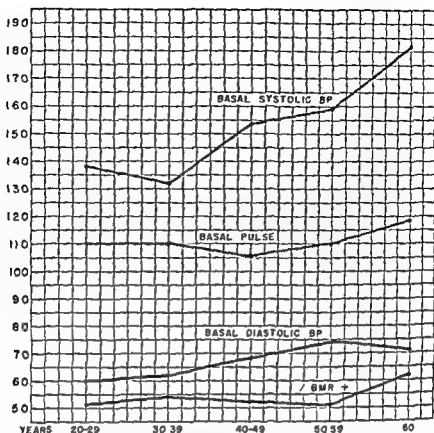


CHART 46 BLOOD PRESSURE IN HYPERTHYROIDISM (See Chart 52 for effect of return of normal thyroid function) Basal BP pulse and BMR plotted according to age groups in cases of hyperthyroidism requiring two-stage operations (severer than average) Note that the average BMR was approximately the same for all age groups while the basal systolic BP, as well as diastolic pressure rose with age (Hurthall L M Blood pressure before and after operation in hyperthyroidism Arch Int Med 47 167 181)



FIG 195 MUSCULAR ATROPHY IN SEVERE HYPERTHYROIDISM (Top) Before treatment (Bottom) After propylthiouracil (Bartels E C and Pizer E Muscular atrophy in hyperthyroidism Report of a case Lahey Clin Bull 4 52 58)

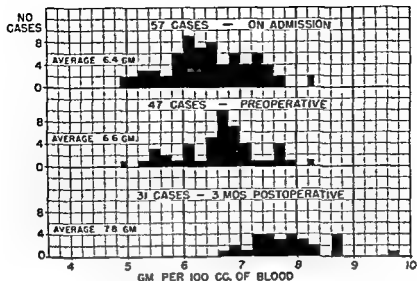


CHART 47 HYPERTHYROIDISM Total serum protein in hyperthyroidism before and after iodine administration and after subtotal thyroidectomy. The shift to the right is caused entirely by the serum albumin fraction. Initial average 3.4 Gm/100 cc. Final average 4.8 Gm/100 cc. (Bartels E. C. Adrenal gland in hyperthyroidism: cortical functions. West J Surg 48: 50-53)



FIG 196 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left) Heart shadow in a young woman age 31 with exophthalmic goiter auricular fibrillation and slight congestive heart failure. Weight 103 lbs. Pulse 93 BP 160/90 BMR plus 101%. Note prominence of pulmonary arc as well as region of left auricle. (Right) Heart shadow 12 months later. Normal rhythm present. Weight 120 lbs. Pulse 84 BP 140/90 BMR plus 11%. Still slightly toxic on Lugol's solution. The outline of each film is superimposed upon the other. Note marked reduction along left side with diaphragm at same level. The prominence of the pulmonary arc persists. (Menard O. J. and Hurxthal L. M. Changes observed on the heart shadow in toxic goiter before and after treatment. Ann Int Med. 6: 1634-1643)

CHART 48

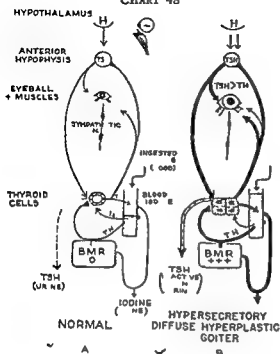
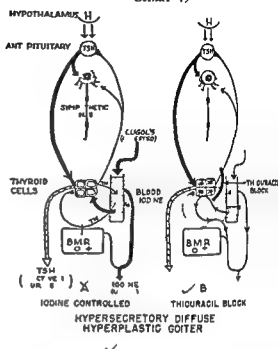


CHART 49



EXPLANATION OF SYMBOLS FOR CHARTS 48-50

- ↑ STIMULATION
 OR DIRECTION
 OF PASSAGE
 ▲ INHIBITION
- INCREASED QUANTITIES OF HORMONE
 □ NORMAL QUANTITIES OF HORMONE
 — PATHWAY BUT NO PASSAGE OF SUBSTANCE

CHART 48 DIAGRAMMATIC PRESENTATION OF VARIOUS RELATIONSHIPS AND PHENOMENA WITH NORMAL AND HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER

A Normal Thyroid Gland

- The original stimulus is pictured as coming from H (hypothalamus) which arouses the pituitary thyrotropic hormone (TSH) to stimulate the thyroid cells represented here by normal resting cuboidal epithelium of one follicle
- TSH is thus utilized and none is excreted in the urine in the active form
- Thyroid hormone (TH)
 - Inhibits and regulates TSH secretion
 - Effects body cells directly
 - Maintains normal metabolism
 - Inhibits thyroid cells
- Iodine
 - Released with utilization of TH by the tissues
 - Sent into the blood stream
 - Broken into smaller fragments by liver excreted in bile reabsorbed by intestine re enters blood stream
 - Reabsorbed by the thyroid cells
 - Excreted in the urine

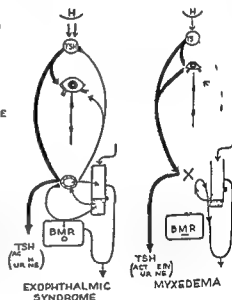


CHART 50

- Ingested iodine contained in diet enters the blood stream and follows same process as liberated iodine (above)
- The normal level of blood iodine and hormone is marked by a block square attached to the container which represents the volume of circulation blood
- Cervical sympathetic system and eyes are so designated
- The whole relationship is normal and in balance

B Hypersecretory Diffuse Hyperplastic Goster

- 1 The hypothetical starting point in this diagram is the hypothalamus
- 2 An excess of TSH is secreted which
 - a Produces changes in the eye and increase in intraorbital fat which may lead to exophthalmos possibly in conjunction with sympathetic system (?)
 - b Causes excessive stimulation of the thyroid cells and hyperplasia
 - c May be present in the urine in inactive form due to effect of thyroid cells
- 3 An excess of TH hormone is produced which
 - a Increases the
 - 1 Urinary iodine excretion
 - 2 Blood iodine (both fractions)
 - 3 BMR
 - b Inhibits the thyroid cells but not sufficiently
 - c May supply additional iodine to the thyroid
- 4 When the disease continues unabated with out an adequate iodine intake the total amount of circulating iodine (free or protein bound) decreases because of its
 - a Quick utilization
 - b Excessive urinary excretion
- 5 At this point there is evidence of an enzyme which facilitates the breakdown of organic iodides which makes them readily available for the thyroid cells but also renders them more liable to loss through the kidneys

CHART 49 DIAGRAMS DEPICTING EFFECT OF IODINE AND THIOURACIL IN HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER.

A Iodine Therapy

- 1 Excess iodine is shown entering the blood stream with a great increase in total blood iodine (mostly inorganic)
- 2 Large amounts are available for thyroid cells which are shown here by four involuted follicles representing hypertrophy as well as previous hyperplasia
- 3 A great excess of iodine is found in the urine
- 4 Since the total output of the whole over active gland would seem to be proportionate to the number of follicles as well as the degree of overactivity it is obvious in this diagram that since the BMR is depicted as normal one of the following phenomena could have taken place
 - a All follicles were overactive and iodine reduced the BMR to normal the thyroid cells (before iodine) may have been functioning to only a half or a third of their ability
 - b Only a part of the follicles were hyperplastic and possibly secreting to their fullest capacity all other follicles being inactive
 - c If the number of follicles was increased but only a part were hyperplastic and

secreting to their fullest extent the others were involuted

- d The reduction of thyroid hormone output by iodine administration in only those follicles which were hyperplastic (the number of which represented only a portion of those present) was sufficient to reduce the metabolism to normal before hyperthyroidism developed (see pp 303 306 and Fig 116 p 341)

B Thiouracil

- 1 Thiouracil preparations block TH production as indicated by short curved heavy black line to right of thyroid cells which are shown as being hyperplastic
 - 2 TSH continues unabated exophthalmos persists
 - 3 The inhibiting effect of TH on TSH is reduced
 - 4 An increase in exophthalmos would be expected but this is not evident by clinical observation except in rare instances
 - 5 Iodine is absorbed by thyroid cells causing a decrease in vascularity and various degrees of involution but apparently is not synthesized into thyroid hormone or its precursors (D and T fractions)
 - 6 The stimulating effect of TH directly on the eyes is also lost which may account for nonprogression of exophthalmos (see above)
- On the other hand TSH administration to animals produces exophthalmos regardless of the removal of the pituitary the thyroid or the gonads. It is obvious that the theory does not fit the facts

CHART 50 DIAGRAMMATIC PRESENTATION OF VARIOUS RELATIONSHIPS AND PHENOMENA IN EXOPHTHALMIC SYNDROME AND PRIMARY MYXEDEMA

A Exophthalmos without Hyperthyroidism

- 1 Excess TSH and its nonutilization or rejection by the thyroid cells is demonstrated
- 2 Urinary TSH is found in the active form
- 3 Exophthalmos is shown
- 4 Thyroid cells are cuboidal
- 5 Blood and urinary iodine are normal
- 6 BMR is normal

B Primary Myxedema

- 1 Excess TSH is present in the blood
- 2 Urinary TSH is found in increased amounts in the active form
- 3 Blood iodine (total and organic) is reduced
- 4 It is difficult to correlate the absence of exophthalmos in myxedematous animals with an excess of TSH
- 5 The above diagrams may also represent a period of myxedema following subtotal thyroidectomy or a stage in the development of endemic goiter
- 6 If spontaneous myxedema is due in some instances to selective deficiency of pituitary TSH excess TSH would not be found in the urine

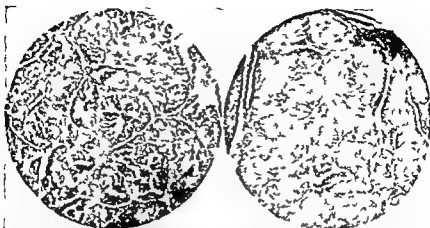


FIG 19. HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left) Low power The microscopic appearance of thyroid gland in severe Graves's disease of long standing. No iodine had been given. The iodine content was 0.3 mg/Gm of dried gland. No colloid is visible. This specimen was obtained by hemithyroidectomy. (Right) Low power. A 11 weeks interval elapsed after the first operation during which time no iodine had been given. The iodine content of this specimen was unchanged. These pictures are representative of a group of patients used as controls in studying the effect of iodine on the hyperplastic gland in Graves's disease (Cattell R. M. The pathology of exophthalmic goitre. Boston M & S J 192 989 996)

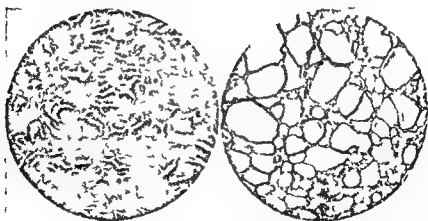


FIG 198. HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left) Low power. Severe hyperthyroidism of 3 years duration with typical hyperplasia. Little colloid can be seen. The iodine content was 0.32 mg/Gm dried gland. (Right) Low power. Six weeks following the administration of Lugol's solution. Complete involution is present with the appearance of a normal or colloid gland. Marked clinical improvement. The iodine content was 5.4 mg/Gm dried gland. Involution is similar but less marked than if thiouracil had been given along with iodine. (Cattell R. M. The pathology of exophthalmic goitre. Boston M & S J 192 989 996)

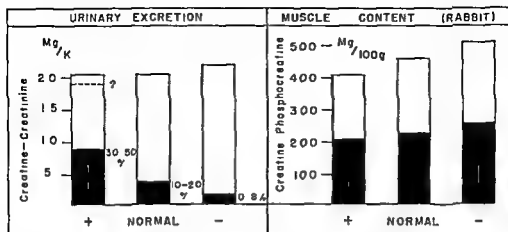


CHART 51 EFFECT OF HYPERTHYROIDISM AND HYPOTHYROIDISM ON URINARY AND MUSCLE CREATINE (Wilkins L. Conferences on Metabolic Aspects of Convalescence 10th Meeting June 15 16 New York Macy p 100)

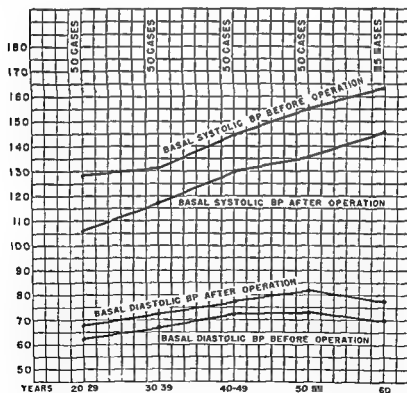


CHART 52 BLOOD PRESSURE IN HYPERTHYROIDISM Effect of subtotal thyroidectomy on average basal BP values 6 to 12 months after operation Plotted by age groups Note rise with age and drop in systolic pressures and rise in diastolic pressures All readings taken at time of metabolism test (Hurxthal L M Blood pressure before and after operation in hyperthyroidism Arch Int Med 47 167 181)

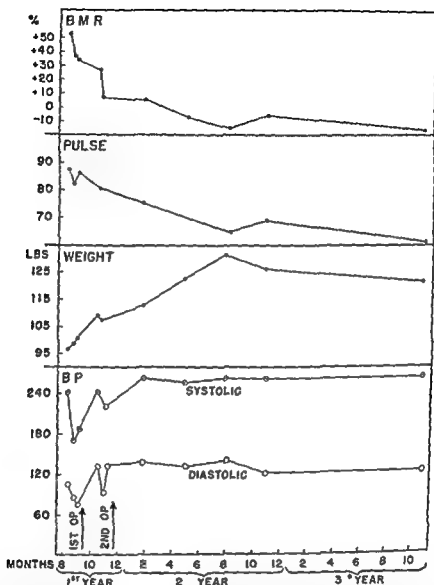


CHART 53 HYPERTENSION AND HYPERTHYROIDISM Observations over a period of 2½ years. Note drop in BP in hospital with bed rest. Subtotal thyroidectomy in 2 stages followed by normal BMR, and pulse rate with a weight gain of 40 lbs. The average diastolic and systolic BPs were higher after operation when hyperthyroidism was relieved completely. (Hurxthal L. M. The heart in hyperthyroidism. *New England J Med* 208: 538-541)

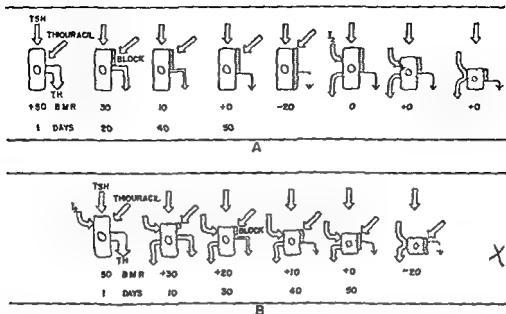


CHART 54 MECHANISM OF THIOURACIL AND IODINE ON THYROID CELLS Schematic representation of relationship between thyroid hormone (TH) and thyrotrophic hormone (TSH). Effect of thiouracil preparations and iodine in hypersecretory diffuse hyperplastic goiter. (A) Upper set of figures shows increasing block produced by thiouracil on hyperplastic thyroid cell. Thiouracil is continued until cell is putting out so little thyroid hormone (TH) that BMR is down to minus 20%. It is then stopped and iodine is given which involutes cell and BMR gradually rises as thyroid hormone is resynthesized and secreted. Dotted cells depict iodine storage. (B) Lower set of figures shows mechanism when iodine and thiouracil are given together. First iodine involutes the cell causing decreased output of thyroid hormone (TH). Thiouracil is then less effective when cells are involuted. Urinary iodine excretion not depicted here except when thyroid cell is saturated with iodine. In all cases when therapeutic doses of iodine are given there is an excess of urinary iodine.

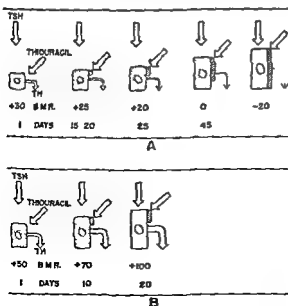
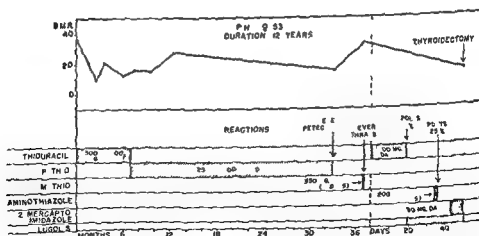
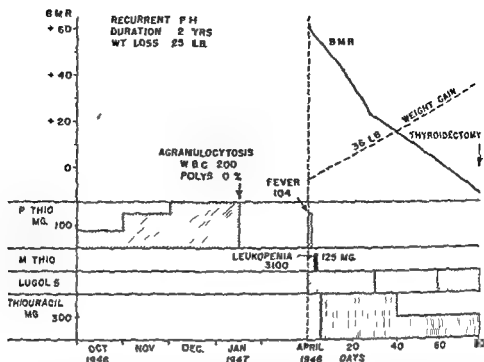


CHART 55 MECHANISM OF THIOURACIL AND IODINE ON THYROID CELLS (A) Schematic representation of effect of thiouracil on iodinated hypersecretory hyperplastic goiter. The partially involuted thyroid cell (cuboidal) is shown gradually becoming hyperplastic (columnar) without further iodine administration. Eventually marked hyperplasia with low BMR. Time required for effect of thiouracil is longer than a non-iodinated gland (45 days for BMR plus 30%). Urinary iodine secretion is not depicted here. (B) Thiouracil administered to very severe case of Graves' disease in or approaching thyroid crisis. Slower action of thiouracil prevents immediate reduction in thyroid hormone output so that death might ensue before thiouracil is effective. Iodine should be given at once.



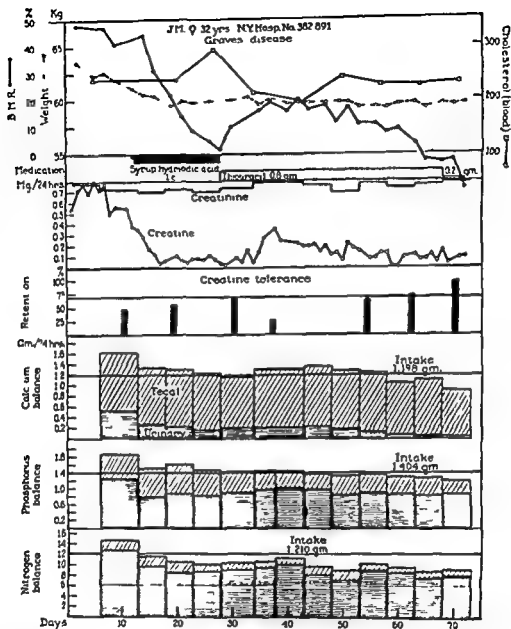


CHART 58 TREATMENT OF HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Use of iodine followed by thiouracil showing relapse while on thiouracil and demonstrating importance of using iodine for quick response and thiouracil for later response in severe hyperthyroidism especially bordering on or in thyroid crisis Note also creatine excretion (Barr D P and Short E Observations on treatment of Graves's disease with thiouracil Ann Int Med 23 754-778)

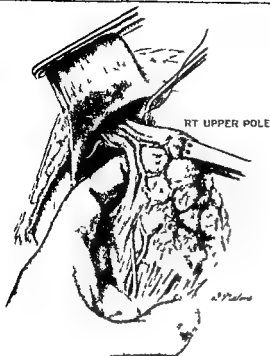
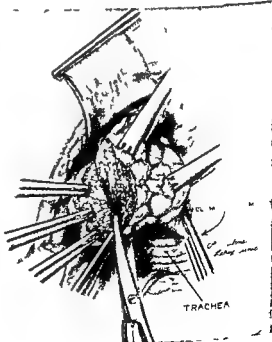
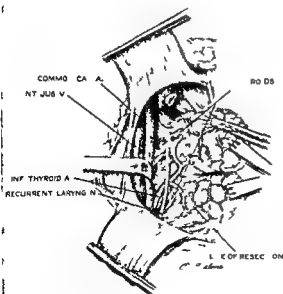


FIG 199 TECHNIC OF SUBTOTAL THYROIDECTOMY Method of separating the upper pole of the thyroid from its attachment to the larynx. The vessels can be completely freed and a ligature passed around them so that it does not include any of the apex of the upper thyroid pole. Note the finger tip placed beneath the upper pole to lift it away from the larynx. This maneuver ensures safe ligation of the superior thyroid artery and vein and even more important permits mobilization of the upper pole of the thyroid away from the larynx. The parathyroid which rests against the

larynx and behind this lobe can be exposed and preserved (Figs 199-201 from Lahey F H. *Technic of subtotal thyroidectomy*. S Clin North America 29:641-658).

FIG 200 (Bottom left) TECHNIC OF SUBTOTAL THYROIDECTOMY The veins between the thyroid gland and the internal jugular vein are completely severed; the gland is lifted out of its bed and the region between the trachea and the common carotid is freed so that the inferior thyroid artery and the recurrent laryngeal nerve are exposed. In this illustration a step is shown which is not done until the lower pole has been mobilized but for the purposes of demonstrating the most common position of the upper parathyroid the superior thyroid pole is demonstrated as severed. The recurrent laryngeal nerve runs over the inferior thyroid artery. Note the relationship of the upper parathyroid and the recurrent laryngeal nerve as it enters the larynx in a position behind the latter where it rests before the superior thyroid artery and vein are severed. The upper pole is mobilized away from the larynx and inward to expose the parathyroid.

FIG 201 (Bottom, right) TECHNIC OF SUBTOTAL THYROIDECTOMY In the outer portion of the illustration the segment of thyroid into which the hemostats are plunged represents the portion of remaining gland. The isthmus is shown as clamped and has been completely separated from the trachea. The section of thyroid previously adherent to the trachea is cut by scissors until the entire lobe on that side is freed. With this portion of the operation completed the entire right lobe of the thyroid (except for the remnant together with the entire isthmus) is removed.



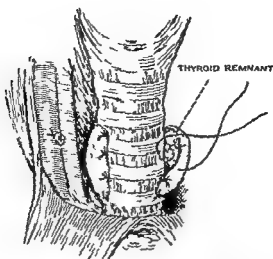


FIG 202 TECHNIC OF SUBTOTAL THYROIDECTOMY This illustration as seen in other technical descriptions of subtotal thyroidectomy shows the remnant of the thyroid which has been sutured against the trachea with 0 catgut stitches between the fascia covering the trachea and the edge of the thyroid The cut surface of the thyroid with all of its tied vessels is sutured against the trachea to control oozing (Lahay F H Technic of subtotal thyroidectomy S Clin North America 29 641 658)

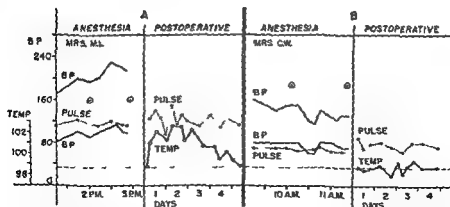


CHART 59 OPERATIVE BEHAVIOR IN HYPERTHYROIDISM A comparison of the anesthetic operative and postoperative course in a patient prepared with (A) Lugol's solution and (B) thiouracil (Bartels E C Thiouracil its use in the preoperative preparation of patients with severe hyperthyroidism S Clin North America 25 645 650)

THYROID DEATHS (2 cases)

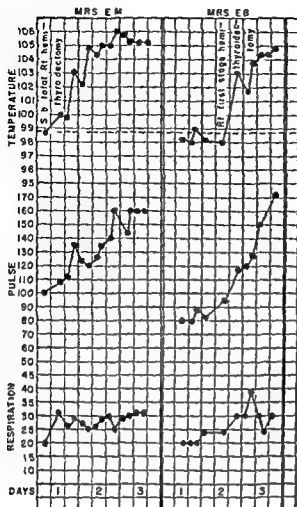
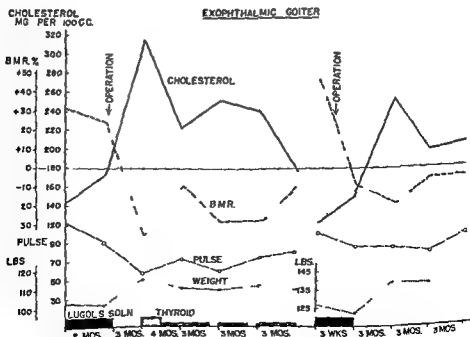


CHART 60 THYROID STORM
Typical postoperative temperature pulse and respiration chart in 2 patients dying in thyroid storm. These are not seen in patients properly prepared with antithyroid drugs

CHART 61 (Bottom) TEMPORARY AND PERMANENT POST OPERATIVE MYXEDEMA. Effect of iodine subtotal thyroidectomy and desiccated thyroid on plasma cholesterol BMR weight and pulse in (1) hypersecretory diffuse hyperplastic goiter subtotal thyroidectomy followed by myxedema requiring desiccated thyroid and (2) hypersecretory diffuse hyperplastic goiter with subclinical thyroid deficiency after subtotal thyroidectomy. No iodine or desiccated thyroid given after operation. The abnormal findings corrected themselves spontaneously. Solid block represents Lugol's solution. Shaded block equals 2 gr of desiccated thyroid (Hurthall L M Blood cholesterol and thyroid disease III Myxedema and hypercholesteremia Arch Int Med 53 :62 1931)



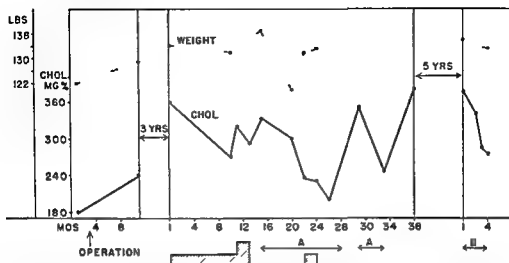


CHART 62 HYPERTHYROIDISM WITH NORMAL PLASMA CHOLESTEROL. Weight 122 lbs Pulse 100 Plasma cholesterol 186 mg % BMR plus 52% BMR after operation was always between minus 6% and minus 11% Plasma cholesterol values as shown No clinical evidence of myxedema Note that weight and plasma cholesterol increased or decreased together except on one occasion

Diagonal lined area = Desiccated thyroid 1 gr daily and a normal diet

Dotted square = Cholesterol (1 Gm a day) dissolved in olive oil

A = Low cholesterol diet (vegetable butter allowed no egg yolk meat fat cream or butter)

B = Egg yolk eliminated

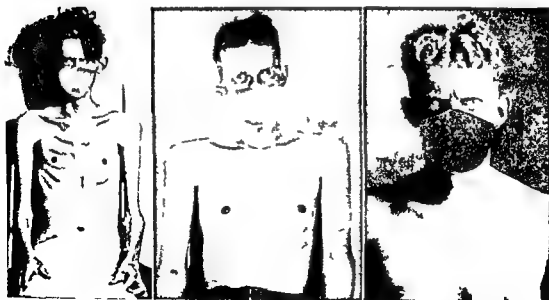


FIG 203 HYPERTHROIDISM DIFFUSE HYPERPLASTIC GOITER (See also Fig 204) Severe hyperthyroidism and thyroid crisis (Left) Before operation (Center) After hemithyroidectomy (Right) Three months after completion of operation Weight gain from 90 to 150 lbs Note absence of chest hair Heart measurements were increased after treatment



FIG 204 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Heart in case shown in Figure 203 Note increase in size of heart shadow Roentgenogram was taken 3 months after final operation



FIG 205 NODULAR GOITER FOLLOWED BY GRAVES'S DISEASE ENOPHTHALMOS ATRIAL FIBRILLATION CONGESTIVE HEART FAILURE PROBABLY RHEUMATIC HEART DISEASE Nodular goiter at 22 years of age without symptoms Treated by radium In complete surgical removal Exophthalmos 4 years later Lugol's solution intermittently for 13 years BMR plus 36% Atrial fibrillation apex rate 148 radial 110 BP 160/80 Weight 129 lbs before disease 113 lbs afterward Subtotal thyroidectomy followed by pulmonary edema fever and death on second postoperative day Pathologic report multiple colloid adenomatous goiter weight 110 Gm with secondary hyperplasia Heart—375 Gm All chambers dilated Left ventricular capacity twice normal Mitral valve rolled thickened and fibrosed considered grossly incompetent Lungs—frothy pink fluid from all bronchi Lower right lung and entire left lung firm and subcrepitant Liver 1200 Gm Cause of death pulmonary edema It would appear that patient had rheumatic heart disease and mitral regurgitation Hearts of this size in hyperthyroidism usually have some coincidental heart disease This case also suggests the development of Graves's disease upon a previous nodular goiter

CLINICAL VARIATIONS OF HYPERTHYROIDISM

Persistent	Associated with diabetes
Recurrent	Associated with pregnancy
Apathetic	Exophthalmic syndrome
Thyrocardiac patient	Factitious

SECTION 27

PERSISTENT HYPERTHYROIDISM

I DEFINITION

- A SUMMARY**—A persistence of hyperthyroid symptoms, although less severe, after medical treatment or surgical removal of seemingly adequate amounts of thyroid tissue
- NOTE** All findings are essentially the same as for hypersecretory hyperfunctioning goiter, except as indicated below

II PHYSICAL STATUS

- A THYROID REMNANTS**—Small to moderate size which are palpable within 3 months or more after operation located in region of isthmus if not previously removed hyperplastic and soft at first then becoming firmer as disease progresses
- B OTHER FINDINGS**—As before operation but less pronounced

III DIAGNOSIS

A SUMMARY

- 1 Borderline cases often present difficult diagnostic problems
- 2 It is important to ascertain if possible whether hyperthyroidism actually existed when the first operation was performed
- 3 If patient is on iodine or an antithyroid drug typical symptoms should become more pronounced when these are discontinued
- 4 A therapeutic trial may establish the diagnosis by using iodine and/or thiouracil because if no improvement follows search for other causes as
 - a Factitious hyperthyroidism
 - b Pheochromocytoma

IV COMPLICATIONS, SEQUELAE AND ASSOCIATED DISEASES

- A GENERAL**—Same as for initial operation, except for greater incidence of¹
- 1 Tetany—2.9 per cent
 - 2 Vocal cord paralysis—14.7 per cent

V TREATMENT

- A COMMENT**—The choice of the following procedures depends on the
- 1 Severity of the case
 - 2 Amount of thyroid tissue
- B MEDICAL**
- 1 Lugol's solution—see 26 \VI B
 - 2 Thiouracil preparations—see 26 \VI D
 - 3 Radioactive iodine—see 26 \VI H
- C ROENTGEN**—see 26 \VI G
- D SURGICAL**—Removal of thyroid remnants may be necessary

VI PROGNOSIS^{2,4}

A COMMENT

- 1 Outcome for permanent cure is less favorable if factors which initiate disorder continue to function
- 2 If cause is inadequate removal of thyroid tissue, results should be same as for subtotal thyroidectomy
- 3 The process may be entirely masked if iodine is administered for first few months postoperatively
- 4 After the introduction of radical thyroidectomies the incidence was lowered
- 5 At present with thiouracil preparations and radical thyroidectomies, no cases have been noted

TABLE 31 OPERATIONS FOR PERSISTENT HYPERTHYROIDISM

TIME	NO OF CASES	PER CENT
Prior to 1927	1016	51
1933-1942	3444	06

Operations done within a 3 year period after first operation. The data reflect the incidence. Approximately 50 per cent of the persistent cases were controlled with iodine.

REFERENCES

1. Cattell R B and Perkin H J. Recurrent hyperthyroidism. The likelihood of recurrence in relation to the preoperative blood iodine level. *Tr Am A Study Goiter* 1938 pp 407-414.
2. Hurxthal L M, Souders C R, DePerin J H and Musulin N. Ten to twenty year results following subtotal thyroidectomy for primary hyperthyroidism: preliminary report on 1016 patients operated upon before 1927. *S Clin North America* 25: 651-656 (June) 1945.
3. ———. Unpublished data.
4. Preston F W and Thompson W O. Persistence and recurrence of toxic goiter following subtotal thyroidectomy. *Arch Int Med* 59: 1019-1039 (June) 1942.

FIG 206 HYPERPLASTIC THYROID REMNANTS IN PERSISTENT AND RECURRENT HYPERTHYROIDISM.

Tips of each thyroid pole are involved. Patient operated upon when it was not customary to remove the poles. Several operations over a 25 year period. Patient controlled with Lugol's solution when photograph was taken. See Chart 61 for effect of thiouracil which produced myxedema and rebound phenomena when medication was discontinued.

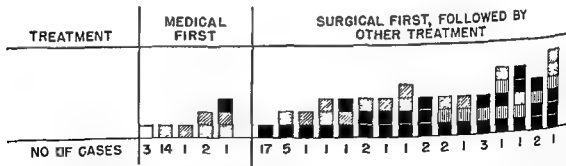


CHART 63 PERSISTENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER. Methods of treatment employed to arrest persistent hyperthyroidism in 1016 cases operated prior to 1927 (589 were followed 10 to 20 years). Each column represents the sequence of events and the number of cases in which this occurred as indicated beneath each column. When one therapeutic procedure is adjacent to another therapeutic procedure it indicates a persistence of hyperthyroidism.

Open square No treatment Black squares Operation
Dotted squares Lugol's solution Diagonal lined squares Roentgen therapy
Vertical lined squares Recurrence

SECTION 28

RECURRENT HYPERTHYROIDISM

I DEFINITION

A SUMMARY

- 1 Recurrent hyperthyroidism may be said to exist when the disease returns following a period of apparent cure or remission after subtotal thyroidectomy or any form of therapy
- 2 Similar pattern as primary disorder except it may be more or less severe
- 3 All the data is the same as under persistent hyperthyroidism except as indicated below

II INCIDENCE

A PAST AND PRESENT DATA¹

- 1 In 1016 cases operated before 1927 589 patients were followed from 10 to 20 years
 - a There were 69 single recurrences or 11 per cent
 - b Some patients had 2 or 3 recurrences
- 2 Other reports show an occurrence of less than 1 to 28 per cent with variable follow up periods^{2 3 4 5 6}
- 3 No data is available on large groups operated upon since 1930
- 4 Sufficient time has not elapsed since antithyroid drugs have been prescribed to evaluate this complication after subtotal thyroidectomy

B OCCURRENCE

- 1 Recurrence may take place in
 - a Few months
 - b Twenty years after the first operation
 - c Any year during the individual's life span
- 2 If more than sufficient thyroid tissue is removed at the first subtotal thyroidectomy resulting in a mild myxedema recurrence of this disorder may be postponed if the individual was destined to have it
- 3 Administration of desiccated thyroid

TABLE 32 RECURRENCE INCIDENCE OF HYPERSECRETORY HYPERPLASTIC GOITER (589 Cases of 1016 Surgical Patients Followed from 10 to 20 Years⁷)

RECURRENCE	NUMBER	PER CENT OF 589 CASES
Once in those living 10 years or more	33	8.99
Once among former permanent cases	13	
Double or triple known among dead before 10 years	7	
Total number of cases	69	11.0
Total recurrent cases are slightly less than the number of recurrences because of double or triple incidences in 7 patients		13.4

following subtotal thyroidectomy might theoretically reduce the stimulus to recurrence¹

III TREATMENT

A MEDICAL

- 1 Lugol's solution
 - a Treatment of choice in mild cases
 - b Disease may be completely alleviated
 - c Myxedema may be produced in rare instances
 - d Thyroid remnants may increase in size although
 - (1) Basal metabolic rate is normal
 - (2) Patient is asymptomatic
- 2 Antithyroid drugs — hyperthyroidism will respond

B ROENTGEN

- 1 Permanent relief of hyperthyroidism by this procedure
- 2 Production of myxedema by roentgen therapy has not cured some cases even when several surgical attempts had failed previously⁸

REFERENCES

- 1 Berlin D D and Gargill M L Factors in fluencing persistent and recurrent hyperthyroidism *New England J Med* 222 254 259 (Feb) 1940
- 2 Bowers H F Recurrent toxic goiter *Tr Am A Study Goiter* 1939 pp 67 74
- 3 Buchbinder W C Some cases of so called 'recurrent thyrotoxicosis' *M Clin North America* 14 1267 1276 (Mar) 1931
- 4 De Courcy J L Prevention of recurrent hyperthyroidism *Ohio State M J* 38 449-451 (May) 1942
- 5 De Courcy J L and De Courcy C B Pathology and Surgery of Thyroid Disease Springfield Thomas 1949 p 403
- 6 Hurxthal L M and Hare H F Unpublished data
- 7 Hurxthal L M Souders C R DePersio J D and Musulin N Ten to twenty year results following subtotal thyroidectomy for primary hyperthyroidism preliminary report on 1016 patients operated upon before 1927 *S Clin North America* 25 651 656 (June) 1945
- 8 Pool E H and Garlock J H Surgical treatment of exophthalmic goiter late end results *Surg Gynec & Obst* 59 330 336 (Sept) 1934
- 9 Preston F W and Thompson W O Persistence and recurrence of toxic goiter following subtotal thyroidectomy *Arch Int Med* 69 1019 1039 (June) 1942
- 10 Thompson W O Morris A E and Thompson P K Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter *Arch Int Med* 46 946 978 (Dec) 1930
- 11 Thompson W O and Preston F W Persistence and recurrence of toxic goiter following subtotal thyroidectomy *Tr Am A Study Goiter* 1941 pp 84 86
- 12 Thompson W O Thompson P K Bailey A G and Cohen A C Myxedema during administration of iodine in exophthalmic goiter *Am J M Sc* 179 733 750 (June) 1930
- 13 Troell A Recurrent goiter from a surgical point of view *Acta chir Scandinav Suppl* 92 1 62 1944
- 14 Young O Recurrent and continuing hyperthyroidism *Am J Surg* 39 104 111 (Jan) 1938



FIG 20/ RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Age 29 BMR plus 78% Subtotal thyroidectomy Weight increased from 113 to 133 lbs BMR's since operation were from minus 12% to plus 1% Note apparent decrease in exophthalmos which was probably due to loss of lid retraction (Left) Before operation (Center) Three months after operation (Right) Ten years later with recurrence of hyperthyroidism

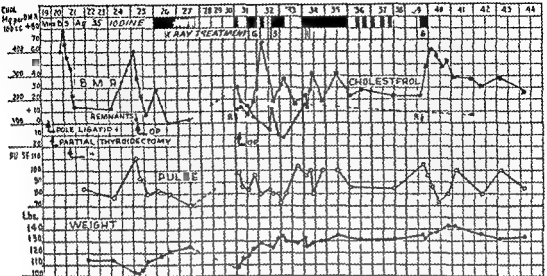


CHART 64 PERSISTENT AND RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER
Observations on a patient over 25 years necessitating 6 operative procedures roentgen ray therapy and iodine Temporary myxedema occurred on several occasions but did not require desiccated thyroid A recurrence of hyperthyroidism was often heralded by the occurrence of paroxysmal auricular fibrillation In spite of the unusual tendency of the underlying cause to persist the patient is in fairly good health today without any therapy Vocal cord paralysis or tetany has not developed This case is representative of a group which fortunately is rare (less than 0.5%)

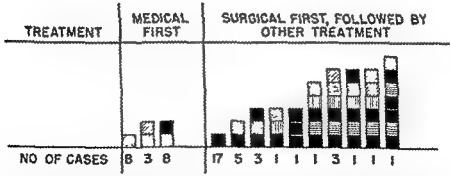


CHART 65 RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER
Methods of treatment employed to arrest recurrent hyperthyroidism in a group among 1016 cases operated upon prior to 1927 580 of which were followed 10 to 20 years Each column shows the sequence of events and the number of cases in which this occurred as indicated beneath each column When one therapeutic procedure is adjacent to another therapeutic procedure it indicates a short interval (i.e. months) of persistent hyperthyroidism between—as opposed to longer intervals when indicated as below
Dotted Lugol's solution
Black Operation
Diagonal lined Roentgen therapy
Vertical lined Recurrence
Horizontal lined Persistence

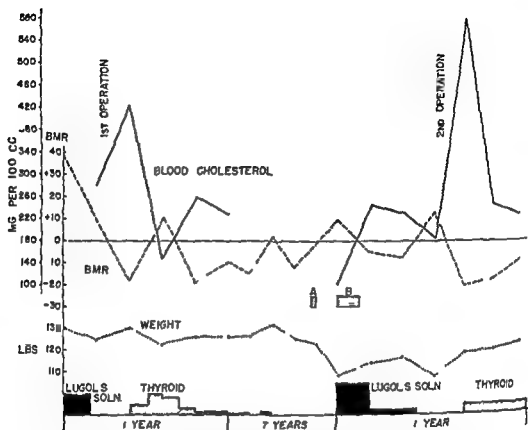


CHART 66 RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER AFTER POST OPERATIVE MYXEDEMA Nine year observations on a patient with Graves's disease who developed postoperative myxedema and gradually a recurrence of thyroid function to the point of hyperthyroidism. A second operation and conservative removal of hyperplastic remnants again resulted in clinical myxedema necessitating the use of desiccated thyroid. Three years later thyroid medication was unnecessary and the patient appeared to have normal thyroid function. Recurrence is possible in view of previous experience.

A Size of thyroid remnant when first palpated

B Two years later approximately 4 times size of A

Desiccated thyroid (U.S.P.) dosage varied from $\frac{1}{4}$ to 4 gr daily. Lugol's solution—3 to 30 minims daily (Hurxthal L. M. Myxedema and its various causes. S. Clin. North America 25: 657-671)

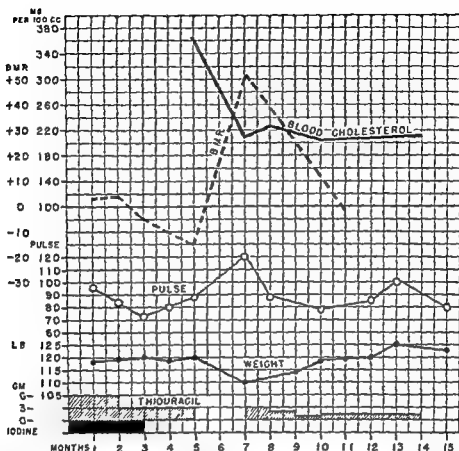


CHART 67 RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Effect of substitution of thiouracil on iodized patient with recurrent hyperthyroidism Temporary myxedema produced Note rebound on discontinuing thiouracil as well as iodine (10 mums daily) and its effectiveness when resumed (Hurxthal L M Myxedema and its various causes 8 Clin North America 25 65, 6:1)

SECTION 29

APATHETIC HYPERTHYROIDISM¹⁻⁶

EYNONYMS Masked hyperthyroidism, *Forme fruste*

- | | |
|--|---|
| I DEFINITION | Hyperthyroidism from hypersecretory nodular or hyperplastic goiter in which the usual characteristics are not evident |
| II APPEARANCE | Apathetic |
| III AGE | Usually older group, but may be seen in the young |
| IV SEX | Predominantly females |
| V PHYSICAL STATUS | |
| A SKIN | Often diffuse tanning, sweating is not excessive |
| B EYES | Exophthalmos appears less frequent |
| C PULSE | May be proportionate or disproportionate to elevation in basal metabolic rate, auricular fibrillation |
| VI LABORATORY DATA | Basal metabolic rate slightly or moderately elevated |
| VII PATHOLOGIC PHYSIOLOGY | |
| A SUMMARY | |
| 1 Patients may represent end result of severe, activated hyperthyroidism | |
| 2 Entity may show loss of | |
| a Tissue (negative nitrogen and calcium balance) | |
| b Adrenocortical anabolic effects | |
| c Ability to react to an excess of thyroid hormone | |
| 3 Associated diseases | |
| a Thyrocardiac disease | |
| b Diabetes mellitus | |
| VIII TREATMENT—see 26 \VI | |

REFERENCES

- | | |
|--|--|
| <p>1 Averbuck S H Masked hyperthyroidism as a cause of heart disease <i>Ann Int Med</i> 16 1011 1018 (May) 1942</p> <p>2 Breidenbach L and Appelbaum E Masked hyperthyroidism <i>Ann Surg</i> 115 184 198 (Feb) 1942</p> <p>3 Hare L, and Ritchey J O Apathetic response to hyperthyroidism report of two cases <i>Ann Int Med</i> 24 634 637 (Apr) 1946</p> | <p>4 Lahey F H Apathetic thyroidism <i>Ann Surg</i> 91 1026 1030 (May) 1931</p> <p>5 — Activated and apathetic hyperthyroidism their importance in cases of heart failure <i>South Surgeon</i> 1 36 38 (Apr) 1932</p> <p>6 Levine S A and Sturgis C C Hyperthyroidism masked as heart disease <i>Boston M & E J</i> 190 233 237 (Feb) 1924</p> |
|--|--|



FIG 208 APATHETIC HYPERTHYROIDISM
Age 59 Apathetic hyperthyroidism with de-
compensation Auricular fibrillation and
ascites Patient lost 11 lbs of water pre-
operatively Weight 86 lbs BMR plus 68%
RBC 3 560 000 Hgb 58%

SECTION 30

THE THYROCARDIAC PATIENT

I DEFINITION

Individuals with hyperthyroidism who have congestive heart failure with regular rhythm, auricular fibrillation or flutter, which are established and not paroxysmal patients with coincidental heart disease without the above specifications not included (see Figs 209, 211 and 212)

II APPEARANCE

Many of the characteristic findings of hyperthyroidism are not evident

III AGE

Average over 50 years 60 per cent over 60, 20 per cent over 50 20 per cent under 50

IV SEX

Females predominate

V PHYSICAL STATUS

A GENERAL

Those found in hyperthyroidism (see 26 VI)

B THYROID

Enlarged, but frequently quite small, firm normal (less than 2%) in size and consistency; adenomatous goiter may be partially or completely substernal, but the latter is rare

C CARDIAC DECOMPENSATION

Edema (may be concealed), liver is enlarged and/or tender, neck veins engorged orthopnea cyanosis

VI ROENTGENOGRAPHIC FINDINGS

Large heart shadow in some thyrocardiac patients is the result of dilatation from congestive heart failure, return to normal size is common in the majority of patients¹⁰

TABLE 33 COEXISTENT CARDIOVASCULAR DISEASE IN THYROCARDIACS (Total—469 Cases⁷)

	CASES No OF
Hypertension noted postoperatively	36
Hypertension (160/90 or more preoperatively)	35
Mitral stenosis (not including patients with apical systolic murmurs and rheumatic history)	27*
Coronary artery disease (clinical)	10
Aortic regurgitation (rheumatic)	2
Aortic stenosis	1
Miscellaneous (congenital acute rheumatic carditis pericarditis)	6

VII ETIOLOGY⁷

A CONGESTIVE HEART FAILURE

- 1 Primary cause—hyperthyroidism
 - a There is a greater incidence of cardiac decompensation in patients with toxic adenoma than diffuse hypersecretory hyperplastic goiter³
 - b Among 7,363 cases of hyperthyroidism, congestive heart failure occurred in 3.7 per cent (around 2.2 per cent in literature)⁸
- 2 Auricular fibrillation or flutter
 - a Precipitating cause in 85 per cent
 - b Heart failure is four times as common in thyrotoxic patients with established auricular fibrillation than with normal rhythm
 - c The incidence for both among 7,363 cases of hyperthyroidism was 5.7 per cent⁸

* In 444 cases of hyperthyroidism without congestive heart failure or auricular fibrillation the number of patients with mitral stenosis was 21 showing only slightly increased incidence in the thyrocardiac group

3 Secondary factors¹

- a Age
- b Coincidental heart disease

4 Inability of the heart to maintain circulatory needs of an increased metabolic rate results in failure even though circulatory rate may be normal

- e Cough
- d Tachycardia
- e Cyanosis
- f Edema
- g Epigastric distress

VIII PATHOLOGY (see 26 \)

A HEART

- 1 Hypertrophy may be³
 - a Slight
 - b Moderate
- 2 Dilatation if death is due to cardiac failure²
- 3 Histologic changes
 - a Nothing specific¹⁶
 - b Brown atrophy and necrosis rarely if ever seen since iodine therapy⁶

IX PATHOLOGIC PHYSIOLOGY

A EFFECT OF HYPERTHYROIDISM ON THE CARDIOVASCULAR SYSTEM

- 1 Blood flow increased (see Charts 68 and 69)
 - a Greater metabolic demands of the tissues and cardiac muscle from direct action of thyroid hormone increase the heart rate independently¹⁷
 - b Peripheral vascular dilatation acts similar to an arteriovenous shunt and more blood flow to thyroid gland adds further to this effect
- 2 Pulmonary pressure is increased which may
 - a Cause a prominent pulmonary arc
 - b Result due to a decreased peripheral and pulmonary vascular resistance producing a piling up effect in the pulmonary artery¹⁰
- 3 Cardiac findings—see 26 \ I A 4

X SYMPTOMATOLOGY

A HYPERTHYROIDISM—see 26 \ II

II CARDIOVASCULAR

- 1 Variable depending on
 - a Degree of decompensation
 - b Severity and duration of disease
 - c Management
- 2 General
 - a Dyspnea
 - b Orthopnea

XI DIAGNOSIS

A HISTORY

- 1 Important in clinical evaluation
- 2 Weight loss in spite of adequate caloric intake

B PHYSICAL STATUS

- 1 It may be difficult to diagnose hyperthyroidism in presence of overshadowing heart symptoms
- 2 Skin
 - a Warm and moist in contrast with dryness in other types of heart disease
 - b Pigmentation may be beyond that which comes with contraction of the skin
- 3 Stare is present even though exophthalmos is absent
- 4 Thyroid gland may be
 - a Enlarged and firm
 - b Normal in size and consistency
 - c Adenomatous and completely substernal which may be detected by roentgenograms of trachea (see 26 VIII F 1)
- 5 Pulse
 - a Rate if not irregular is above normal except occasionally in men
 - b Pressure increased
- 6 Tremor not diagnostic

C LABORATORY DATA—Basal metabolic rate is elevated with

- 1 Congestive failure
- 2 Cardiac compensation
- 3 Aortic stenosis (complicated)

XII DIFFERENTIAL DIAGNOSIS

A MITRAL STENOSIS—Description

- 1 Rumbling diastolic murmur
- 2 Presystolic crescendo culminating in a booming first sound

II HYPERTENSIVE HEART DISEASE WITH CONGESTIVE FAILURE

- 1 While an elevated diastolic pressure may be present in hyperthyroidism it is rare

- 2 Left ventricular hypertrophy may be marked
 - 3 Decision must rest on evaluation of other signs and/or symptoms
 - 4 Basal metabolic rate may also be elevated (see 44 VII E 1)
- C MISCELLANEOUS**
- 1 Hyperthyroidism may occur with any type of cardiovascular disease capable of ending in congestive failure
 - 2 Paroxysmal auricular fibrillation or flutter that develops in the presence of coincidental heart disease (especially mitral stenosis) may cause
 - a Respiratory distress
 - b Acute decompensation

XIII TREATMENT

A GENERAL—see 26 \VI

B ACUTE CONGESTIVE HEART FAILURE WITH THYROID CRISIS

- 1 Medications—dosage
 - a Digitalis preparations
 - (1) Initial (intravenous)—calculated per 15 lbs of body weight in patients who have not had this medication for 2 to 3 weeks previously

(a) Digalen	1 cc
(b) Digoxin	0.1 mg
(c) Digatoxin	0.02 mg
(d) Lantoside C	0.4 mg
 - (2) Procedure—amounts as above repeated in 6 hrs if needed and tolerated
 - (3) Maintenance (oral)

(a) Digitalis	1.5 gr
(b) Digoxin	0.5 mg
(c) Digatoxin	0.1 mg
(d) Lantoside C	1.0 mg
 - b Strophantin (ouabain)
 - (1) Intravenous 0.5 mg initially if no digitalis taken by patient for 10 days previously
 - (2) Procedure 0.1 mg every half hour until ventricular rate is below 80/min
 - (3) Maximum No more than 1 mg should be given in 24 hrs

- c Mercurial diuretics
 - (1) Indication—marked edema
 - (2) Dosage—1 to 2 cc intravenously
- d Morphine— $\frac{1}{8}$ to $\frac{1}{4}$ gr hypodermically, every 3 hrs as necessary
- 2 Management (see 26 \VI M 1)
 - a Restrict fluids to 3 000 cc. per day if given intravenously, administer very slowly
 - b Salt should not be used
 - c Venesection (400 to 600 cc) is indicated, if cyanosis is not relieved by oxygen
 - 3 Result—unless severity of hyperthyroidism cannot be abated, acute congestive failure can be adequately eliminated

C CHRONIC CONGESTIVE HEART FAILURE

- 1 Medication (see Charts 70 73)
 - a Digitalize patient within 24 to 72 hrs (see above)
 - b Acid salts such as ammonium chloride
 - (1) Useful
 - (2) Dosage—15 gr q.i.d. orally
 - c Theophyllin or mercurial diuretics if needed
- 2 Management (see 26 \VI)
 - a If cyanosis is not relieved by oxygen venesection (400 to 600 cc) is indicated
 - b Diet
 - (1) Salt free or no added salt
 - (2) Acid ash
 - 3 Results
 - a Mild to moderate congestive failure will cease with
 - (1) Bed rest, occasionally
 - (2) Bed rest plus iodine sometimes
 - (3) Antithyroid drugs, usually
 - b It is desirable to treat both hyperthyroidism and congestive failure simultaneously

D AURICULAR FIBRILLATION OR FLUTTER (see Charts 70 and 75)

- 1 Quinidine
 - a Indication—if auricular fibrillation persists and when the patient has been properly prepared with an antithyroid drug it is not likely to recur
 - b Dosage
 - (1) Oral initially 3 gr t.i.d. p.c. for one day

- 3 Secondary factors⁴
 - a Age
 - b Coincidental heart disease
- 4 Inability of the heart to maintain circulatory needs of an increased metabolic rate results in failure even though circulatory rate may be normal

VIII PATHOLOGY (see 26 V)

A HEART

- 1 Hypertrophy may be³ & 14 17
 - a Slight
 - b Moderate
- 2 Dilatation if death is due to cardiac failure³
- 3 Histologic changes
 - a Nothing specific¹⁶
 - b Brown atrophy and necrosis rarely if ever seen since iodine therapy⁶

IX PATHOLOGIC PHYSIOLOGY

A EFFECT OF HYPERTHYROIDISM ON THE CARDIOVASCULAR SYSTEM

- 1 Blood flow increased (see Charts 68 and 69)
 - a Greater metabolic demands of the tissues and cardiac muscle from direct action of thyroid hormone increase the heart rate independently¹⁸
 - b Peripheral vascular dilatation acts similar to an arteriovenous shunt and more blood flow to thyroid gland adds further to this effect
- 2 Pulmonary pressure is increased which may
 - a Cause a prominent pulmonary arc
 - b Result due to a decreased peripheral and pulmonary vascular resistance producing a piling up effect in the pulmonary artery¹⁰
- 3 Cardiac findings—see 26 VI A 4

X SYMPTOMATOLOGY

A HYPERTHYROIDISM—see 26 VII

B CARDIOVASCULAR

- 1 Variable depending on
 - a Degree of decompensation
 - b Severity and duration of disease
 - c Management
- 2 General
 - a Dyspnea
 - b Orthopnea

- c Cough
- d Tachycardia
- e Cyanosis
- f Edema
- g Epigastric distress

XI DIAGNOSIS

A HISTORY

- 1 Important in clinical evaluation
- 2 Weight loss in spite of adequate caloric intake

B PHYSICAL STATUS

- 1 It may be difficult to diagnose hyperthyroidism in presence of overshadowing heart symptoms
 - 2 Skin
 - a Warm and moist in contrast with dryness in other types of heart disease
 - b Pigmentation may be beyond that which comes with contraction of the skin
 - 3 Stare is present even though exophthalmos is absent
 - 4 Thyroid gland may be
 - a Enlarged and firm
 - b Normal in size and consistency
 - c Adenomatous and completely substernal which may be detected by roentgenograms of trachea (see 26 VIII F 1)
 - 5 Pulse
 - a Rate, if not irregular is above normal except occasionally in men
 - b Pressure increased
 - 6 Tremor not diagnostic
- ### C LABORATORY DATA—Basal metabolic rate is elevated with
- 1 Congestive failure
 - 2 Cardiac compensation
 - 3 Aortic stenosis (compensated)

XII DIFFERENTIAL DIAGNOSIS

A MITRAL STENOSIS—Description

- 1 Rumbling diastolic murmur
- 2 Presystolic crescendo culminating in a booming first sound

B HYPERTENSIVE HEART DISEASE WITH CONGESTIVE FAILURE

- 1 While an elevated diastolic pressure may be present in hyperthyroidism it is rare

- 13 Menard O J and Hurxthal L M Changes observed in the heart shadow in toxic goiter before and after treatment *Ann Int Med* 6 1634 1643 (June) 1933
- 14 Parkinson J and Cookson H Size and shape of heart in goitre *Quart J Med* 24 499 532 (July) 1931
- 15 Phillip J R and Milliken E Total thyroidectomy in the treatment of angina pectoris *Am J Surg* 43 125 126 (Jan) 1939
- 16 Rake G and McEachern H Study of heart in hyperthyroidism *Am Heart J* 8 19 21 (Oct) 1932
- 17 Wilhus F A Boothby W M and Wilson L B The heart in exophthalmic goiter and adenoma with hyperthyroidism *M Clin North America* 71 189 219 (July) 1923

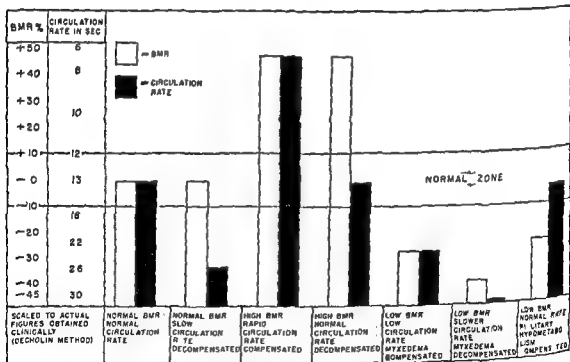


CHART 68 CIRCULATION RATES IN VARIOUS CONDITIONS WITH ABNORMAL METABOLIC RATES
Schematic relationship between circulation rate and BMR in normal hyperthyroid myxedematous and hypopituitary persons. The circulation time is increased in hyperthyroidism and when the heart cannot keep up with the demands of a high BMR cardiac failure develops eventually. (Hurxthal L M Frank Howard Lahey—*Birthday Volume Springfield Ill Baltimore pp* 245 269)

- (2) Procedure

If not effective, 6 gr are given tid pc until paroxysmal auricular fibrillation stops, medication discontinued if any unpleasant symptoms arise
- (3) Intravenous

Rarely needed
- 2 Morphine only can be used to quiet patient if there is no cardiac embarrassment

ment

E TOTAL THYROIDECTOMY FOR HEART DISEASE¹⁻⁹

- 1 Practice abandoned

a There may be rare circumstances when it might still be applied

b Best results in chronic heart failure from rheumatic heart disease or angina pectoris¹⁻¹³
- 2 Lessons learned

a Complete ablation is necessary to produce myxedema

b Myxedema eventually causes a poorer cardiac function, thus a return of original signs and symptoms
- 3 The excellent theory that desiccated thyroid can be given after total ablation to prevent full blown myxedema but at the same time to relieve cardiac symptoms has not been proved sufficiently from actual experience to warrant its continued use
- 4 Radioactive iodine is now being tried

XIV PROGNOSIS

- 4 MORTALITY OF THYROID SURGERY IN THYROCARDIACS

1 Prethiouracil era (1922 to 1941)—614 cases (6.6%)

2 Thiouracil era (1943 to 1947)—none

TABLE 34 STATUS OF 469 OPERATED CASES (1922 TO 1941, AT 1942 FOLLOW UP¹)

Known alive	306
Excellent	201
Good	100
Poor	5
Known dead	165
Untraced	143
Postoperative myxedema	14 (2.9%)
Persistent auricular fibrillation (in good group of known alive)	84 (27%)

B LIFE EXPECTANCY AND OUTCOME

- 1 After successful surgery, 50 per cent of normal expectancy (based on 469 cases followed 10 to 15 years⁷)

2 Persistent auricular fibrillation

a Life expectancy in thyrocardiacs does not decrease (see Chart 73)¹¹

b After subtotal thyroidectomy, may subside spontaneously
- 3 Recurrent congestive heart failure is rare without

a Recurrence of hyperthyroidism

b Severe coincidental heart disease
- 4 Angina may be entirely relieved after subtotal thyroidectomy

REFERENCES

1 Berlin D D, Riseman J E F, and Blumgart H L. The present status of total thyroidectomy. *Tr Am A. Surg* 1940 pp 1-6

2 Blumgart H L, Freedberg A S and Buka R. Treatment of euthyroid cardiac patients by producing myxedema with radioactive iodine. *Proc Soc Exper Biol & Med* 67 190-191 (Feb) 1948

3 Brenner O. Thyroid gland and heart disease. *Brit M J* 2 199 205 (Aug) 1935

4 Cutler E C and Hoerr S D. Total thyroidectomy for heart disease. 5 year follow up study. *Ann Surg* 113 245 259 (Feb) 1941

5 Ertelene A C. Heart in hyperthyroidism. *M Clin North America* 17 923 937 (Jan) 1934

6 Goodpasture E W. Myocardial necrosis in hyperthyroidism. *JAMA* 76 1545 (June) 1921

7 Greece A M and Hurxthal L M. Postopera-

tive follow up study of 469 thyrocardiac patients. *New England J Med* 225 811 816 (Nov) 1941

8 Hurxthal L M. *Thyrocardiac*. F H Lahey Birthday Volume Springfield Thomas 1940 pp 245-269

9 Hurxthal L M and Claiborne T S. Results of total thyroidectomy in heart disease. *New England J Med* 216 411 417 (Mar) 1937

10 Hurxthal L M, Menard O J and Bogan M H. Size of heart in goiter tolerant: genographic study. *Am J M Sc* 180 77-781 (Dec) 1930

11 Lahey F H, Hurxthal L M and Driscoll R E. Thyrocardiac disease: review of 614 cases. *Ann Surg* 118 681 693 (Oct) 1943

12 Lakoff W B and Levine S A. Thyrotoxicosis as the sole cause of heart failure. *Am J M Sc* 205 425-434 (Oct) 1943

FIG 210 HEART SHAD
OWS IN THYROCARDIAC
PATIENT (See also Chart
71) Graves disease of
17 years duration in a
male with auricular fibril
lation and congestive
heart failure (Left)
Roentgenogram of chest
on admission to hospital
(Right) Eighteen days
later, and before opera
tion (Hurxthal L M
Heart failure and hyper
thyroidism with special
reference to etiology,
Am Heart J 4 103
108)

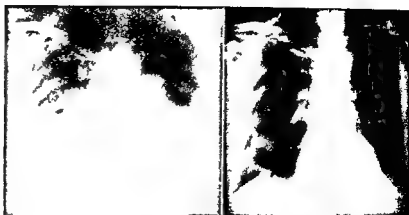


FIG 211 THYROCARDIAC PATIENT Congested
neck veins in a thyrocardiac Nodular goiter
auricular fibrillation hyperthyroidism and con
gestive heart failure



FIG 212 THYROCARDIAC PATIENT Age 51
female with severe hyperthyroidism showing
emaciation exophthalmos and enlarged thy

roid Congestive heart failure auricular fibril
lation and orthopnea BMR plus 49% Weight
94 lbs Weight loss 50 lbs in 2 years Patient
survived bilateral pole ligation Died suddenly
2 days postoperatively with fever rising to
105 F Postmortem examination revealed a
heart weighing 320 Gm dilated especially on
right side Pericardium obliterated by numer
ous delicate fibrous adhesions Myocardium
flabby and brownish color showed a few large
fibers and slight amount of granular precipi
tate in interstitial tissue Adrenals had diminu
tion of cortical lipid Lymph glands consid
ered enlarged Thymus not found Lungs
revealed no foci of pneumonia mucopurulent
secretion in bronchi Liver 1080 Gm ap
peared normal except for indistinct lobules
Many cells revealed vacuolization No necrosis
lobules smaller than normal Remaining lobe of
thyroid weighed only 15 Gm majority of
acini lined with flattened epithelium filled with
colloid Numerous papillary ingrowths with
columnar epithelium Death was assigned to
heart failure which was probably true in view
of its suddenness The high fever and the
purulent bronchial secretion are frequent find
ings in those dying of thyroid storm The peri
carditis rather than hyperthyroidism was prob
ably the cause of such great hypertrophy in
the absence of valvular disease and hyperten
sion



FIG 209 THYROCARDIAC PATIENT (*Top*) Age 51 female Hyperplastic goiter auricular fibrillation and severe congestive heart failure with anasarca Duration of goiter 17 years Symptoms of hyperthyroidism 10 years Weight 219 lbs BMR plus 45% After preoperative preparation weight 142 lbs RBC 3.2 million Hgb 54% NPN 34 mg % blood chlorides 495 mg % After diuresis RBC 4.0 to 5.6 million Hgb 85% serum protein 9.1 and 8.9 Gm % blood chlorides 443 mg % (*Bottom*) Three months after last operation She had a pole ligation and 2 hemithyroidectomies Edema free no dyspnea Weight 146 lbs Pulse 54 (auricular fibrillation) BMR minus 5% Multiple stage operations are unnecessary with thiouracil treatment In cases with such severe anasarca diuretics and digitalis should still be employed while waiting for the effect of anti thyroid drugs

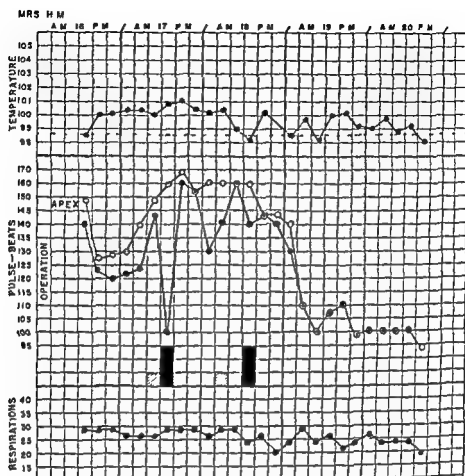


CHART 70 DIGITALIS THERAPY IN PAROXYSMAL AURICULAR FIBRILLATION
 Effect in intravenous digitalis (digalen) on paroxysmal auricular fibrillation occurring after subtotal thyroidectomy. Hospital chart. Ordinarily paroxysmal auricular fibrillation causes no respiratory difficulty but in this case a patent ductus arteriosus was present and patient was given digitalis because of orthopnea.
 Diagonal lined areas = 3 gr. of digitalis leaf. Solid areas = 3 ampules of digalen.

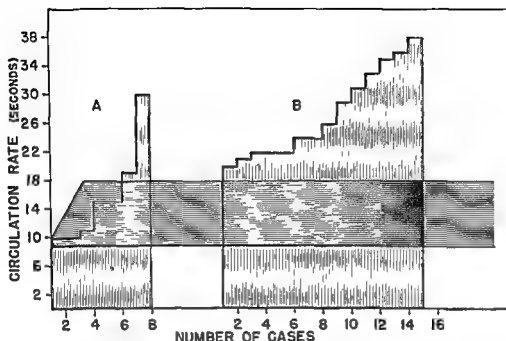


CHART 69 CIRCULATION RATES IN CONGESTIVE FAILURE Normal zone shown by horizontal shaded area (A) In hyperthyroid patients with congestive failure (B) In nonhyperthyroid patients with congestive failure Note normal values in all cases of hyperthyroidism except 2 patients (7 and 8) in whom there was severe congestive failure (i.e. anasarca hydrothorax etc) Most hyperthyroid patients without congestive failure have circulation rates below 12 sec and occasionally as low as 6 sec See Chart 68 for relationship between BMR and circulation rate in hyperthyroidism (arm tongue with decholin) (Hurxthal L M and Claiborne T S Unpublished data)

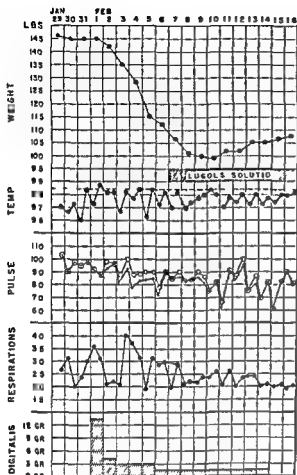


CHART 72 (Left) THYROCARDIAC—EFFECT OF DIGITALIS AND BED REST Hospital chart of a woman age 30 with nodular goiter hyperthyroidism, rheumatic heart disease with mitral regurgitation and slight stenosis Auricular fibrillation present Note weight remained level with rest in bed alone Digitalis given by mouth was followed by a diuresis of 35 lbs Note continuation of diuresis when Lugol's solution was begun and then a gain of real weight (nitrogen retention?) amounting to 8 lbs The pulse rate here was not exceptionally fast BMR on admission plus 48% Patient was operated upon in 2 stages Auricular fibrillation ceased patient gained 37 lbs and fully recovered (Hurxthal L M The heart in hyperthyroidism New England J Med 208 538 541)

CHART 73 (Right) THYROCARDIAC PATIENTS WITH NORMAL RHYTHM AND AURICULAR FIBRILLATION AFTER OPERATION Ratio of thyrocardiac patients having normal rhythm and persistent auricular fibrillation and the effect on rate of survival over period of 10 to 20 years It appears that auricular fibrillation does not influence survival rate in this group In most instances patients with auricular fibrillation received digitalis (Lahey F H Hurxthal L M and Driscoll R M Thyrocardiac disease a review of 614 cases Ann Surg 118 681 691)

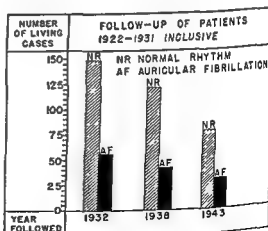




CHART 71 THYROCARDIAC—EFFECT OF DIGITALIS LUGOL'S SOLUTION AND BED REST (See also Fig 210) Chart of patient male age 42 with exophthalmic goiter and severe congestive heart failure. No pulse or BP could be obtained on admission to hospital. Note drop in heart rate on digitalis and rest alone. Lugol's solution given on eighth day. Note sudden loss of 10 lbs of edema following its use. Metabolism test was not done on admission. His pulse later became regular before operation and without quinidine. The patient's critical condition on admission was the result of heart failure rather than thyroid toxicity although the latter was the cause of the former. There was a marked reduction in the size of the cardiac shadow after recovery from failure and after auricular fibrillation had ceased (Hurxthal L M. The heart in hyperthyroidism. *New England J Med* 208:528-541).

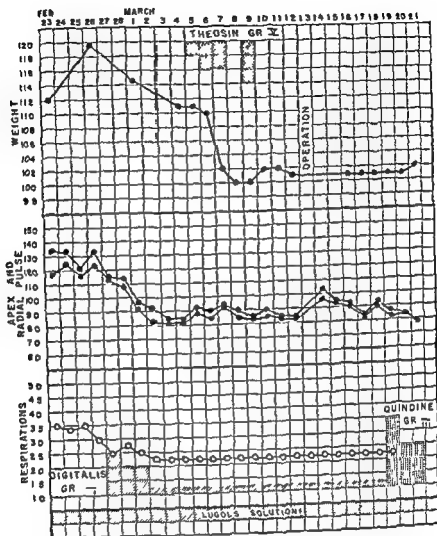


CHART 15 THYROIDCARDIAC—THERAPY INCLUDING QUINIDINE SULFATE
 Chart showing results of bed rest digitalis theosin and quinidine in a case of toxic adenomatous goiter with auricular fibrillation and congestive heart failure Female age 55 BMR plus 25% Note increase in edema on Lugol's solution and bed rest then diuresis and slowing of pulse after digitalis (each square represents 3 gr digitalis leaf) Further diuresis after theosin (each square represents 5 gr orally) Pulse became regular on third day of quinidine therapy (each square represents 3 gr quinidine sulfate orally) (Hurxthal L M The heart in hyperthyroidism New England J Med 208 538 541)

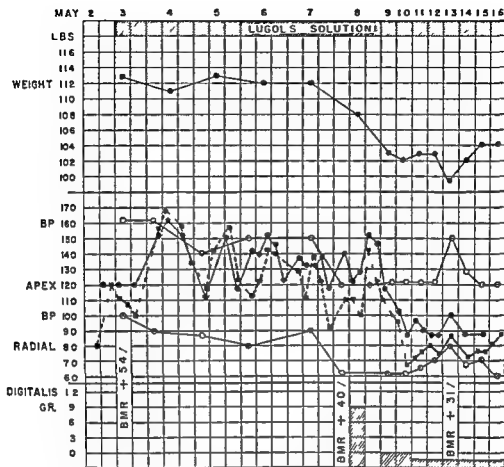


CHART 74 THYROCARDIAC—THERAPY OF CONGESTIVE FAILURE Effect of bed rest and Lugol's solution on patient with hypersecretory hyperplastic goiter and congestive heart failure. Note that there was very little change in weight until digitalis was given. However, this may be due to a combination of retention of fluid for anabolic processes with actual reduction of cardiac and other edema from the effects of iodine. Yet the rapid drop in heart rate with digitalis shows its effectiveness. Postmortem examination of heart showed no abnormality. Weight 300 Gm. (This is a hospital chart and it is obvious that the initial observations on apex and radial pulse were in error.)

- Greater tendency in hyperthyroid patient
- 3 Weight
 - a Most patients gain
 - b Polyphagia because of high metabolism is eliminated by control of hyperthyroidism
- 4 Insulin
 - a Smaller or larger amounts will be required
 - b Some may need it at a later date
- 5 Basal metabolic rate drops as in hyperthyroidism alone
- 6 Mortality rate (prethiouracil era)—2.4 per cent

VII PROGNOSIS¹⁷

- A SUMMARY—Essentially the same as diabetic cases without hyperthyroidism

VIII CAUSES OF DEATH

A SUMMARY

- 1 Postoperative hyperthyroidism or shock

- 2 Diabetic coma
- 3 Same as for diabetes—see 84 XVIII
- 4 Cardiac failure
- 5 Pneumonia
- 6 Septicemia (gangrene, carbuncles)
- 7 Cerebral arteriosclerosis

REFERENCES

- 1 Holst J Glycosuria and diabetes in exophthalmic goitre *Acta med Scandinav* 55 302 (June) 1921
- 2 John H J Hyperthyroidism showing carbohydrate metabolism disturbances 10 year study and follow up of cases *JAMA* 99 620 627 (Aug) 1932
- 3 Joslin E P and Lahey F H Diabetes and hyperthyroidism *Am J M Sc* 176 122 (July) 1928
- 4 — Diabetes and hyperthyroidism *Ann Surg* 100 629 637 (Oct) 1934
- 5 Joslin E P et al *The Treatment of Diabetes Mellitus* Philadelphia Lea & Febiger 1946 pp 725 735
- 6 Regan J F and Wilder R M Hyperthyroidism and diabetes *Arch Int Med* 65 1116 1122 (June) 1940
- 7 Wilder R M *Clinical Diabetes Mellitus and Hyperinsulinism* Philadelphia Saunders 1940 pp 244 261

SECTION 31

HYPERTHYROIDISM AND DIABETES MELLITUS

I DEFINITION

A patient with characteristics of hyperthyroidism and diabetes mellitus the significant features of this combination only are mentioned here otherwise refer to specific chapters

II AGE

Average age of onset of diabetes in diffuse hypersecretory hyperplastic goiter is 41.5 adenoma with hyperthyroidism is 50.2³

III LABORATORY DATA

A URINE

Normal or glycosuria^{1 5 6 7}

B BLOOD SUGAR (fasting)

Normal or increased^{1 5 6 7}

C GLUCOSE TOLERANCE TEST

Curve is not dependent on severity of case impaired function in 66 per cent of all cases of hyperthyroidism

D BASAL METABOLIC RATE

Increased

IV ETIOLOGY

A FACTORS—It is not known definitely whether or not hyperthyroidism causes diabetes

V PATHOLOGIC PHYSIOLOGY

A LIVER

- 1 Glycogen content is poor because of failure to convert or store glucose for tissue demand is so great
- 2 Damage is not chief factor in hyperglycemia

B RENAL THRESHOLD

- 1 Low in patients with hyperthyroidism
- 2 Severity of the disease bears no relationship
- 3 Glycosuria is found in
 - a Mild or severe cases with or without diabetes
 - b Postoperative patients unless adequately controlled with diet and/or insulin

C PANCREAS

- 1 Insulin brings improvement by
 - a Glycogen storage
 - b Decrease in ketone bodies
 - c Protein sparing action
- 2 Hyperglycemia in hyperthyroidism
 - a Unrelated to severity of disease
 - b Incidence—0.5 to 90.0 per cent (average 18.31%)^{1 5 6 7}

TABLE 35 INCIDENCE^{1 5 7}

CASES	RANGE PER CENT	AVERAGE PER CENT
Hyperthyroidism discovered in diabetics	0.97-3.0	1.68
Diabetes mellitus found in hyperthyroidism	0.5-4.3	2.31
	PER CENT GLYCOSURIA (Incidence—1.0 to 38.6)	PER CENT DIABETES
Hypersecretory diffuse hyperplastic goiter	33.6	1.7 and 2.5
Adenomatous goiter with secondary hyperthyroidism	27.7	4.3 and 5.6

VI TREATMENT

A GENERAL—see 26 VII

B RESULTS AFTER SUBTOTAL THYROIDECTOMY

- 1 Carbohydrate tolerance improves if not then
 - a Diabetic management is inadequate
 - b Infection may be present
 - c Other complications should be sought
- 2 Diabetes mellitus may develop after surgery due to
 - a Insufficient removal of thyroid tissue
 - b Specific factors that can produce it

TABLE 37 OUTCOME OF 16 PREGNANT WOMEN TREATED WITH ANTITHYROID DRUGS, IODINE AND SUBTOTAL THYROIDECTOMY DURING FIRST TWO TRIMESTERS*

NO OF CASES	MOTHERS	BABIES
11	Normal deliveries	Normal
1	Abortion at 5 months	Died
1	Premature delivery	Stillbirth
1	Premature delivery	Died 8 hrs later
1	Eclampsia	Stillbirth at term
1	Cesarean section	Died 4 hrs later

IV PROGNOSIS

A HYPERTHYROIDISM (untreated)

- 1 Some patients may

- a Improve in latter months of pregnancy or postpartum
- b Become worse
- c Have other pregnancies without any difficulty

- 2 The majority do fairly well with proper management
- 3 "Latent" or unrecognized hyperthyroidism may become manifest at parturition

B PREGNANCY (treated or untreated)

- 1 Normal^{1 10 25 8 3 45}
- 2 Abortion—see Table 37
- 3 Stillbirth—see Table 37^{2 1 18 21 4}
- 4 Fetal goiter
- 5 Thyroid deficiency in fetus⁴

REFERENCES

- 1 Baer J L Basal metabolism in pregnancy and the puerperium *Am J Obst & Gynec* 2 249 256 (Sept) 1921
- 2 Bell G O Hyperthyroidism pregnancy and thiouracil drugs *JAMA* 144 1243 1246 (Dec) 1950
- 3 Bothe F A Hyperthyroidism associated with pregnancy *Am J Obst & Gynec* 25 628 632 (Apr) 1933
- 4 — Hyperthyroidism associated with pregnancy *Ann Surg* 101 422 428 (Jan) 1935
- 5 Boys C E Goitre in pregnancy *J Michigan M Soc* 22 511 515 (Dec) 1923
- 6 Bram I Exophthalmic goiter and pregnancy *Am J Obst & Gynec* 3 352 358 (Apr) 1922
- 7 Clute H M and Daniels D H Hyperthyroidism and pregnancy *Am J M Sc* 179 477-482 (Apr) 1930
- 8 Croom Halliday J Exophthalmic goiter in its relation to gynaecology and obstetrics *J Obst & Gynaec Brit Emp* 11 368 369 1907
- 9 Daly P A and Strouse S Thyroid during pregnancy clinical observations *JAMA* 84 1798 1800 (June) 1925
- 10 Davis L J and Forbes W Thiouracil in pregnancy effect on foetal thyroid *Lancet* 2 740 742 (Dec) 1945
- 11 Doderlein G Experimenteller Hyperthyreoidismus und seine Wirkung auf Fortpflanzung und Nachkommenschaft *Arch f Gynak* 133 680 719 1928
- 12 Eaton J C Treatment of thyrotoxicosis with thiouracil *Lancet* 1 171 174 (Feb) 1945
- 13 Falls F H Hyperthyroidism complicating pregnancy *Am J Obst & Gynec* 17 536 549 (Apr) 1929
- 14 Fleischer A Thyrotoxicosis complicated by pregnancy *Am J Obst & Gynec* 22 273 276 (Aug) 1931
- 15 Frazier C H and Ulrich H F Pathology of the thyroid gland complicating pregnancy *Am J Obst & Gynec* 24 870 879 (Dec) 1932
- 16 Freiesleben E and Kjerulf Jensen K Effect of thiouracil derivatives on fetuses and infants *J Clin Endocrinol* 7 47 51 (Jan) 1947
- 17 Frisk A E and Josefson E Thiouracil derivatives and pregnancy *Acta med Scandinav Suppl* 196 pp 85 91 1947
- 18 Gardiner Hill H Pregnancy complicating simple goitre and Graves disease *Lancet* 1 170 174 (Jan) 1929
- 19 Hertz J On Goitre and Allied Diseases Especially Thyrotoxicosis with Particular Reference to the Surgical Treatment Copenhagen Munksgaard London Oxford 1943 pp 325 333
- 20 Hughes E C Study of 1 250 basal metabolisms during pregnancy clinical presentation of cases *New York State J Med* 34 873-880 (Oct) 1934
- 21 Hyman H T and Kessel L Studies of exophthalmic goiter and involuntary nervous system relationship to sex life of female *JAMA* 4 88 2032 2034 (June) 1927
- 22 Jackson A S Hyperthyroidism complicating pregnancy *Ann Clin Med* 2 303 311 (Mar) 1924
- 23 Javert C T Hyperthyroidism and pregnancy *Am J Obst & Gynec* 29 954 953 (June) 1940
- 24 Kibel I Hyperthyroidism and pregnancy *Am J Obst & Gynec* 48 553 556 (Oct) 1944
- 25 King R W and Collen F Thiouracil in treatment of hyperthyroidism complicating pregnancy presentation of 2 cases *Permanent Found M Bull* 5 15 16 (Mar) 1947
- 26 Markoe J W Abstract of discussion on L F Watson's Goiter in Pregnancy *JAMA* 71 877 878 (Sept) 1918
- 27 McLaughlin C W and McGoogan L S Hyperthyroidism complicating pregnancy *Am J Obst & Gynec* 45 591 603 (Apr) 1943
- 28 Mussey R D The thyroid gland and pregnancy *Am J Obst & Gynec* 36 579 588 (Sept) 1938
- 29 Mussey K D Haines S F and Ward E Hyperthyroidism and pregnancy *Am J Obst & Gynec* 55 609 618 (Apr) 1948
- 30 Mussey R D and Plummer W A Treatment of goiter complicating pregnancy *JAMA* 97 602 605 (Aug) 1931
- 31 Mussey R D Plummer W A and Boothby W M Pregnancy complicating exophthalmic

SECTION 32

HYPERTHYROIDISM AND PREGNANCY

I DIAGNOSIS

A SUMMARY

- 1 Hyperthyroidism may develop at any stage of pregnancy
- 2 Last trimester

■ The diagnosis of this complication aside from physical signs, will require an increase of at least plus 30 per cent or more in the basal metabolic rate^{19 20 21}

- a Normally there is about a 25 per cent increase (falls to normal after parturition) which is due to the (1) Fetal^{1 20 22}

(a) Thyroid (may be functioning)^{23 24}

(b) Size

- (2) Maternal tissue changes to a lesser degree²⁵

- 3 Vomiting of hyperthyroidism may be mistaken for hyperemesis gravidarum²⁶
- 4 Conception rarely occurs in hyperthyroid patients^{27 28 29}

- 2 Hyperthyroidism or cretinism rarely occurs^{37 41}

- 3 Goiter may develop

- 4 Thiouracil in milk is harmful to newborn rats²³

III TREATMENT

A MANAGEMENT

- 1 Hyperthyroidism is treated first and not the pregnancy

- 2 Induced abortion is contraindicated^{4 15 22}

- a Hyperthyroidism is not relieved
- b Thyroid crisis may result

- 3 Antithyroid drugs and iodine in preparation for subtotal thyroidectomy (see 26 XVI E)³⁰

- a Management same as for nonpregnant women

- b Subtotal thyroidectomy is safe in first two trimesters none reported in last trimester

- c Results—effective^{10 16 22 24}

- 4 Antithyroid drugs without thyroidectomy

- a Basal metabolic rate should be kept around plus 20 to plus 30 per cent until term

- b Careful observation for thyroid deficiency (i.e. hypercholesterolemia)

- c Program as outlined below may be desirable to prevent fetal loss

- d Patient should not nurse while taking antithyroid drugs

- 5 After subtotal thyroidectomy during pregnancy, the following program seems justified until term

- a Desiccated thyroid—1 to 2 gr orally daily

- b Lugol's solution—5 drops orally daily in chocolate milk after meals

- c Stilbestrol (see 60 II J) if evidence of

- (1) Threatened abortion
- (2) Toxemia

- 6 Premature delivery or cesarean section has been performed before antithyroid drug era not recommended now^{3 14 4}

TABLE 36 INCIDENCE^{4 7 23 24 26 27 31 34 39}

	PERCENTAGE
Pregnancy complicated by hyperthyroidism	0.5 to 1.4
Hyperthyroidism complicated by pregnancy	0.4 to 0.6

II COMPLICATIONS

A MATERNAL

- 1 Abortion or premature delivery (54.5%)^{18 30}

- 2 Difficult and prolonged labor taxes the heart

- 3 Postpartum hemorrhage^{6 8 43}

- 4 Tracheal compression if nodular goiter

- 5 Thyroid crisis during

- a Labor

- b Postpartum

- Toxemia of pregnancy²

B FETAL

- 1 Infant's health is normal^{25 3 37 45}

SECTION 33

EXOPHTHALMIC SYNDROME

- I DEFINITION**
The presence of unexplained unilateral or bilateral exophthalmos with little or no evidence of hyperthyroidism or enlargement of the thyroid gland. If progressive to an undesirable degree, exophthalmos is termed malignant.
- II APPEARANCE**
Normal looking individual except for unilateral or bilateral prominence of the eyes and usually without enlargement of the thyroid gland (see Figs 213 and 214).
- III AGE**
Variable
- IV SEX**
Males predominate in ratio of 4:1,¹⁵ malignant postoperative exophthalmos develops more often in men.
- V PHYSICAL STATUS**
- A EYES**
Exophthalmos of variable degree unilateral or bilateral may be complicated by conjunctivitis, excessive lacrimation (epiphora), diplopia, external ophthalmoplegia, periorbital edema, chemosis of conjunctivae (excessive edema of ocular conjunctiva), acute swelling of lids, blepharitis, corneal ulcer, keratinization of conjunctivae, orbital infection, blindness from optic atrophy or papilledema, panophthalmitis.
- B THYROID**
Normal or slightly enlarged.
- C OTHER SIGNS**
May be present as in hyperthyroidism or none at all, except the above.
- VI LABORATORY DATA**
- A URINE**
Labeled (radioactive) iodine excreted in greater amounts than in primary hyperthyroidism.¹⁶
- B BLOOD CHEMICAL ANALYSES**
- 1 Cholesterol (plasma)
Normal
- 2 Iodine (protein bound)
Normal³⁰
- C BASAL METABOLIC RATE**
Normal, decreased or slightly increased.
- D URINARY HORMONE ASSAY**
Thyrotropic hormone (TSH) excreted in active and in active form.²⁷⁻²⁹ Level in blood may be high.³
- VII ETIOLOGY**
- A UNKNOWN**
- B POSSIBLY SAME FACTORS AS IN HYPER THYROIDISM—see 26 IX**
- VIII PATHOLOGY**
- A THYROID**
- 1 Normal
- 2 Same as in mild hyperthyroidism—see 26 X A 1, B 1
- B EYES**
- 1 Gross
- a Extrinsic muscles are swollen in some cases from 3 to 8 times the normal size, causing increased intra orbital tension.³²
- b Orbital fat markedly increased.³³
- 2 Microscopic—muscles show
- a Edema
- b Round cell infiltration
- c Loss of structure
- d Fragmentation
- e Hyalinization
- f Fibrous tissue in increased amounts

goutter and adenomatous goutter with hyperthyroidism J.A.M.A 87 1009 1012 (Sept) 1926

32 Palmer M V Hyperthyroidism and thiouracil Ann Int Med 22 335 364 (Mar) 1945

33 Plass E D and Yoakum W A Basal metabolism studies in normal pregnant women with normal and pathologic thyroid glands Am J Obst & Gynec 18 556 563 (Oct) 1929

34 Portis B and Roth H A Diagnosis and treatment of hyperthyroidism associated with pregnancy J.A.M.A 113 895 898 (Sept) 1939

35 Sandiford I and Wheeler T Basal metabolism before during and after pregnancy J Biol Chem 193 329 352 (Dec) 1924

36 Seitz L Die Störungen der inneren Sekretion in ihren Beziehungen zu Schwangerschaft Geburt und Wochenbett Verhandl d deutsch Gesellsch f Gynak, 15 213-475 1913

37 Setton D L Thiouracil clinical evaluation following 7 1/2 years experience South M J 11 891 897 (Nov) 1946

38 Soule M D Study of thyroid activity in normal pregnancy Am J Obst & Gynec 23 165 171 (Feb) 1932

39 Stepto R C Thyrotoxicosis and pregnancy West J Surg 54 317 319 (Aug) 1946

40 Strouse S and Drabkin C Hyperthyroidism in pregnancy treated with thiouracil J.A.M.A 131 1494 1495 (Aug) 1946

41 Wallace J T Thyrotoxicosis in its relation to pregnancy Am J Obst & Gynec 26 77 83 (July) 1933

42 Watson L F Goutter in pregnancy J.A.M.A 71 875 878 (Sept) 1918

43 White C Exophthalmic goutter and pregnancy labour and the puerperium J Obst & Gynaec Brit Emp 20 126 132 1911

44 — A foetus with congenital hereditary Graves disease J Obst & Gynaec Brit Emp 21 231 233 1912

45 Whitelow M J Thiouracil in the treatment of hyperthyroidism complicating pregnancy and its effects on the fetus Assn of Int Secretions 29th Program June 1947 p 37

46 Williams J W Obstetrics ed 5 New York Appleton 19 567

47 Williams R H Thiouracil treatment of thyrotoxicosis results of prolonged treatment J Clin Endocrinol 6 1 22 (Jan) 1946

48 Williamson A C Pregnancy following thyroidectomy Am J Obst & Gynec 14 196 202 (Aug) 1927

49 Yoakum W A Thyroid gland in pregnancy clinical study in region of endemic goutter Am J Obst & Gynec 15 617 626 (May) 1928

- 9 Sympathetic nervous system is hyperactive
- 10 Thyrotropic hormone
 - a Overproduction
 - b Inhibition decreased
- 11 Hypothalamic origin¹³

X SYMPTOMATOLOGY

- A GENERAL (see 26 VII)
 - 1 None referable to clinical hyperthyroidism *per se*
 - 2 Eyes
 - a Prominence
 - (1) Progressive
 - (2) Sudden
 - b Blurring vision
 - c Diplopia
 - d Photophobia
 - e Epiphora
 - f Ophthalmoplegia
 - g Pains and/or aching
 - h Tenseness
 - i Pressure
 - j Lack of parallelism
 - k Smarting

XI DIAGNOSIS

- A EXOPHTHALMOS
 - 1 Variable degrees
 - 2 Either
 - a Bilateral
 - b Unilateral
- B THYROID—Normal size usually, enlarged rarely
- C LABORATORY DATA
 - 1 Iodine (protein bound)—normal
 - 2 TSH (urinary)—positive
 - 3 Basal metabolic rate
 - a Normal
 - b Decreased
 - c Increased slightly

XII DIFFERENTIAL DIAGNOSIS

- A HYPERTHYROIDISM
 - 1 Eyes may be less
 - a Edema
 - b Irritative phenomena
 - 2 Thyroid gland—enlarged
 - 3 Iodine (protein bound)—increased
 - 4 Thyrotropic hormone (TSH) (urinary)—negative
 - 5 Basal metabolic rate—elevated
 - 6 Radioactive iodine is

- a Taken up very readily by thyroid gland¹
- b Excreted in smaller quantities

B FACTITIOUS HYPERTHYROIDISM

- 1 History may be obtained of self medication
- 2 Lid retraction rarely exophthalmos
- 3 Basal metabolic rate—increased

C NEUROCIRCULATORY ASTHENIA—see 26 XIV A

D SCHULLER CHRISTIAN'S SYNDROME

- 1 Diabetes insipidus
- 2 Bone defects
 - a Skull deformities
 - (1) Geographical map
 - (2) Bone rarefaction
 - (3) Both tables involved
 - b Cysts in
 - (1) Long bones
 - (2) Pelvis
 - c Fractures
 - (1) Spontaneous
 - (2) Compressed
- 3 Exophthalmos may be quite marked
- 4 Xanthoma dissemination (Each of the first 3 findings are combined with No 4 or all 3 occur with it)

E ALL FORMS OF EXOPHTHALMOS—The following group should be considered and usually may be identified by cone roentgenographic study of the orbits

- 1 Tumors or inflammation of bony wall of orbit
- 2 Diseases of nasal accessory or vascular sinuses
 - a Arteriovenous aneurysms
 - b Thrombophlebitis of cavernous sinus
- 3 Intracranial tumor
- 4 Malignant hypertension (uncommon)
- 5 Acromegaly (rare)
- 6 Cushing's syndrome (occasionally)

XIII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A COMPLICATIONS AND SEQUELAE

- 1 Blindness
- 2 Corneal ulceration
- 3 Extension of lens
- 4 Panophthalmia
- 5 Ophthalmoplegia
- 6 Optic edema
- 7 Necrosis (?)

- Pallor
- h Rubbery hardness
- i Lymphorrhages (infiltrations of lymphocytes with some plasma and endothelial cells)⁸

IX PATHOLOGIC PHYSIOLOGY

A GENERAL (see Chart 50, p 479)

- 1 The underlying conditions leading to the pathologic and physiologic changes are unknown
- 2 Rare as a primary disorder
- 3 Development frequently following therapeutic arrest of hyperthyroidism
- 4 Occurrence years later is possible without recurrence of hyperthyroidism
- 5 Malignant exophthalmos is found in less than 1 per cent of all cases

B THYROID GLAND

- 1 Exophthalmos is found in postoperative cases of hyperthyroidism, therefore thyroid gland is not the primary factor⁹
- 2 Idiopathic exophthalmos occurs in the absence of thyroid disease

C THYROTROPIC HORMONE

- 1 Excessive amounts of this hormone in blood and urine may or may not cause exophthalmos³
- 2 Spontaneous myxedema does not produce this syndrome in spite of increased amounts of TSH
- 3 A balance normally exists between TSH and thyroid hormone in relation to water storage
 - a If this mechanism is altered the orbit may be affected because of its structure
 - b Significance to edema of ocular muscles debatable
- 4 Injections of TSH (also anterior pituitary extracts) in various animals^{10 11 17 20 37 38 49 53 54 57 58}
 - a Exophthalmos is produced in many species regardless of
 - (1) Thyroidectomy (more severe and readily produced)
 - (2) Hypophysectomy
 - (3) Sympathectomy
 - b Younger animals develop exophthalmos more often
 - Thyrotropic induced exophthalmos in guinea pigs becomes worse during

a refractory period especially in those with low basal metabolic rates¹⁰

d Fat globules are produced in⁸

- (1) Muscles
 - (a) Ocular
 - (b) Cardiac
 - (c) Skeletal
- (2) Liver
- (3) Epithelial cells
- (4) Phagocytes in
 - (a) Lungs
 - (b) Spleen
 - (c) Lymph nodes

e Muscles

- (1) Pale
- (2) Edematous
- (3) Lymphocytic infiltration
- (4) Scar tissue

f Increase in

- (1) Lipoids (plasma)
- (2) Acetone (blood)

D SYMPATHETIC SYSTEM

- 1 Role is not known in this syndrome
- 2 In humans cervical sympathetic stimulation causes no protrusion of eye balls except when exophthalmos is already present¹⁰

E DRUGS PRODUCING EXOPHTHALMOS

- 1 Potassium thiocyanate given for hypertension
- 2 Sulfathiazole (rats)—hyperplastic goiter produced also
- 3 Methyl cyanide (rabbits)

F SUMMARY OF THEORIES ON EXOPHTHALMOS

- 1 Retro ocular fat increased^{9 40 4 51 5}
- 2 Edematous infiltration of^{19 0 51 5 50}
 - a Fat
 - b Orbital contents
- 3 Dilatation of capillaries^{14 44 60}
- 4 Distention of retro ocular veins
- 5 Contracture of smooth muscles³⁰
 - a Muller
 - b Hesser
 - c Landstrom
- 6 Backward pull of ocular muscles is decreased
- 7 Cellular infiltration and enlargement of extra-ocular muscles^{2 3 33 53}
- 8 Normal restraint of eyeballs is decreased because of wide-open lids i.e. lid retraction

- (7) All available bone is taken out
 - (a) The lateral wall of the orbit well down into the temporal fossa
 - (b) The posterior and inferior wall beyond the sphenoid ridge into the middle fossa to the superior orbital fissure
 - (c) Remaining orbital wall is taken away superiorly
 - (d) Optic foramina are uncapped, while medially and superiorly the bony removal is carried to the ethmoid and the frontal sinuses
 - (8) The periorbital fascia is incised in a stellate pattern, allowing the edematous orbital tissues to be decompressed
 - (9) Hemostasis is secured by ballooning out the dura with subdural saline solution
 - (10) Sulfon powder is used liberally
 - (11) Small tissue drains are left superficially
 - (12) Bone flaps are tied with black silk
 - (13) Scalp tissues sutured through out with interrupted black silk
 - (14) Bilateral operation may be performed
- c Postoperative management
- (1) Dressings are done daily with the usual precautions taken in any routine craniotomy
 - (a) These are removed gradually to avoid pain
 - (b) Patients are sensitive to light
 - (c) White ointment is applied
 - (d) Area is covered with a strip of gutta serena or boric acid which is doubled over the sponges to keep moisture in eyes
 - (e) Warm solutions are ordered after first week
 - (f) Small flaxseed poultices are used to
 - [1] Absorb moisture
 - [2] Exert pressure from their own weight (substituted for sponges)
 - (2) Drains are removed second day
 - (3) Scalp sutures are taken out the third day
 - (4) Lid sutures are taken out in 6 to 7 days
 - (5) Puffiness of lids is last to recede
 - (6) All bandages are removed from 7 to 10 days postoperatively
 - (7) Pressure is continued nightly for 2 to 3 weeks, depending on degree of conjunctival reaction
- d Results^{1 2 3 4 5 6}
- (1) Eyes may show immediate and marked recession
 - (2) Ocular movements may
 - (a) Return to normal
 - (b) Remain the same
 - (c) Become worse
 - (3) Diplopia may
 - (a) Disappear
 - (b) Diminish
 - (c) Remain the same
 - (d) Be corrected by
 - [1] Lenses
 - [2] Minor operative therapy
 - (4) Improvement in
 - (a) Vision
 - (b) Visual fields
 - (c) Corneal ulcers
- e Complications
- (1) Wound infections
 - (2) Cerebrospinal rhinorrhea
 - (3) Meningitis
 - (4) Frontal lobe symptoms (temporary)
 - (a) Confusion
 - (b) Delirium
 - (c) Semiconsciousness
 - (d) Disorientation
- f Outcome (35 cases at Lahey Clinic)
- (1) Satisfactory—31 (see Fig 214)
 - (2) Unfavorable—4
- 2 Radical external ethmoidectomy has given satisfactory results⁴⁸
 - 3 Subtotal thyroidectomy is not recommended because exophthalmos may increase^{15 18 19 20 47}
 - 4 Bilateral cervical sympathectomy—results are poor
 - 5 Hypophysectomy (partial)—may be effective, but is not recommended

- 8 Entire eye or eyes protrude beyond lids

II ASSOCIATED DISEASES

- 1 Myxedema
- 2 Hypertension
- 3 Neurocirculatory asthenia it may be difficult to exclude hyperthyroidism

XIV TREATMENT

A MEDICAL

- 1 Desiccated thyroid in large doses may be tried, but temporary or slight improvement at best¹
- 2 Lugol's solution—not effective except when slight degree of hyperthyroidism may exist
- 3 Lugol's solution and desiccated thyroid^{38 47}
 - a Lugol's solution in doses of 10 to 30 minims daily (rational questionable)
 - b Desiccated thyroid is given simultaneously in sufficient dosage with out producing excessive hyperthyroidism
 - c Diuretic action of thyroid is not opposed by iodine
- 4 Radioactive iodine
 - a Experimental use only at present
 - b Further increase in severe exophthalmos is not observed⁴⁸
 - c No indication unless it effects pituitary TSH secretion
- 5 Thiouracil^{1 49 51}
 - a Indication—to replace iodine
 - b Dosage—as in hyperthyroidism
 - c Results—variable but generally poor
- 6 Stilbestrol¹ or testosterone
 - a Indication—to inhibit pituitary
 - b Results—questionable

B ROENTGEN

- 1 Pituitary or orbit may be treated^{1 21 36 42 43}
- 2 Dosage over pituitary
 - a Initially—200 r for 5 to 7 days
 - b Later—repeat in 2 or 3 months if there is no improvement
- 3 Results usually disappointing

C LOCAL²

- 1 Prevention of
 - a Scratching of scleras
 - b Infection

2 Medications for infection

a Penicillin

- (1) Ointment 500 to 800 units /Gm
- (2) Saline solution 500 to 1,000 units/cc
- (3) Allergy in 12 per cent

b Chloromycetin

- (1) One half per cent solution
- (2) Preferred therapy

c Sulfonamides

- (1) Sulfadiazine 5 per cent ointment
- (2) Sulfathiazole 5 per cent ointment
- (3) Sulfanilamide 0.8 per cent in Ringer's solution

d Cortisone—see 107 VIII M 4

- 3 Anesthetic solutions are contraindicated if corneal epithelium is denuded because the following would occur

- a Delay in healing
- b Scarring

D SURGERY FOR MALIGNANT EXOPHTHALMOS

- 1 Operative procedure on eyes (Naffziger's method)^{31 45}

- a Optimal time for operation is before the occurrence of
 - (1) Severe chemosis
 - (2) Corneal ulceration

b Technic

- (1) Eyelids are sutured immediately before decompression
- (2) A coronal incision is made the skin flap is reflected to the supra orbital ridges
- (3) Two small triangular osteoplastic flaps are turned down
- (4) Dura is then separated from the orbital plate to the sphenoid ridge
- (5) A small portion of the lateral wall of the frontal bone adjacent to the orbital plate is removed away to allow for easier exposure
- (6) A burr opening is made over the lateral margin of the roof of the orbit

- (7) All available bone is taken out
 - (a) The lateral wall of the orbit well down into the temporal fossa
 - (b) The posterior and inferior wall beyond the sphenoid ridge into the middle fossa to the superior orbital fissure
 - (c) Remaining orbital wall is taken away superiorly
 - (d) Optic foramina are uncapped, while medially and superiorly the bony removal is carried to the ethmoid and the frontal sinuses
 - (8) The periorbital fascia is incised in a stellate pattern, allowing the edematous orbital tissues to be decompressed
 - (9) Hemostasis is secured by ballooning out the dura with subdural saline solution
 - (10) Sulfa powder is used liberally
 - (11) Small tissue drains are left superficially
 - (12) Bone flaps are tied with black silk
 - (13) Scalp tissues sutured through out with interrupted black silk
 - (14) Bilateral operation may be performed
- c Postoperative management
- (1) Dressings are done daily with the usual precautions taken in any routine craniotomy
 - (a) These are removed gradually to avoid pain
 - (b) Patients are sensitive to light
 - (c) White ointment is applied
 - (d) Area is covered with a strip of gutta percha or boric acid which is doubled over the sponges to keep moisture in eyes
 - (e) Warm solutions are ordered after first week
 - (f) Small flaxseed poultices are used to
 - [1] Absorb moisture
 - [2] Exert pressure, from their own weight (substituted for sponges)
 - (2) Drains are removed second day
 - (3) Scalp sutures are taken out the third day
 - (4) Lid sutures are taken out in 6 to 7 days
 - (5) Puffiness of lids is last to recede
 - (6) All bandages are removed from 7 to 10 days postoperatively
 - (7) Pressure is continued nightly for 2 to 3 weeks, depending on degree of conjunctival reaction
- d Results^{1 2 3 4 5 6}
- (1) Eyes may show immediate and marked recession
 - (2) Ocular movements may
 - (a) Return to normal
 - (b) Remain the same
 - (c) Become worse
 - (3) Diplopia may
 - (a) Disappear
 - (b) Diminish
 - (c) Remain the same
 - (d) Be corrected by
 - [1] Lenses
 - [2] Minor operative therapy
 - (4) Improvement in
 - (a) Vision
 - (b) Visual fields
 - (c) Corneal ulcers
- e Complications
- (1) Wound infections
 - (2) Cerebrospinal rhinorrhea
 - (3) Meningitis
 - (4) Frontal lobe symptoms (temporary)
 - (a) Confusion
 - (b) Delirium
 - (c) Semiconsciousness
 - (d) Disorientation
- f Outcome (35 cases at Lahey Clinic)
- (1) Satisfactory—31 (see Fig 214)
 - (2) Unfavorable—4
- 2 Radical external ethmoidectomy has given satisfactory results¹⁵
 - 3 Subtotal thyroidectomy is not recommended because exophthalmos may increase¹⁵ 7 8 17 55
 - 4 Bilateral cervical sympathectomy—results are poor
 - 5 Hypophysectomy (partial)—may be effective but is not recommended

XV PROGNOSIS

A TYPES

- 1 Limited or benign—fair
 - 2 Unlimited or malignant
 - a Rapid progress
 - b Blindness from postoperative
- (1) Papilledema

(2) Optic atrophy

(3) Corneal ulceration

XVI CAUSES OF DEATH

A INTRACRANIAL EXTENSION OF INFECTION FROM EYES

B NATURAL

REFERENCES

- 1 Adler F H Role of exophthalmos in diagnosis and treatment of Graves disease (report of cases) West Virginia M J 40 316 326 (Oct) 1944
- 2 Beetham W P Personal communication
- 3 Brain W R and Mann I Discussion on exophthalmos and endocrine disturbance Proc Roy Soc Med 38 666 670 (Oct) 1935
- 4 Cattell R B Eye complications in exophthalmic goiter cataracts and exophthalmos Ann Surg 100 341-353 (Aug) 1934
- 5 — Unpublished data
- 6 Chapman E M and Evans R D Treatment of hyperthyroidism with radioactive iodine JAMA 131 86 91 (May) 1946
- 7 de Robertis E Assay of thyrotropic hormone J Clin Endocrinol 8 956 966 (Nov) 1948
- 8 DeBryns H M Influence of thyroidectomy on prominence of eyes in guinea pig and in man Surg Gynec & Obst 80 526 533 (May) 1945
- 9 Dudgeon L S and Urquhart A L Lymphorhages in muscles in exophthalmic goitre Brain 49 182 186 (June) 1926
- 10 Friedgood H B Clinical applications of studies in experimentally induced exophthalmos of anterior pituitary origin J Clin Endocrinol 1 804 812 (Oct) 1941
- 11 — Experimental exophthalmos and hyperthyroidism in guinea pigs clinical course and pathology Bull Johns Hopkins Hosp 54 48 73 (Jan) 1934
- 12 Gail Mammis C Exophthalmometric measurements in patients with thyroid diseases with some discussion of their significance Ann Int Med 16 415 426 (Mar) 1942
- 13 Gwyner I Druger M and Iowenstein O Exophthalmos and associated ocular disturbances in hyperthyroidism Arch Ophth 37 211 219 (Feb) 1947
- 14 Grace R V and Weeks C Surgery of the thyroid in a large municipal hospital Ann Surg 113 496 507 (Apr) 1941
- 15 Hertz M Means J H and Williams R H Graves disease with dissociation of thyrotoxicosis and ophthalmopathy West J Surg 49 493-498 (Sept) 1941
- 16 Hertz S and Roberts A Radioactive iodine as an indicator in thyroid physiology V The use of radioactive iodine in the differential diagnosis of two types of Graves disease J Clin Investigation 21 31 32 (Jan) 1942
- 17 Hogben L Studies on internal secretion I The effect of pituitary (anterior lobe) injection upon normal and thyroidectomized animals Proc Roy Soc London A B 94 204 215 (Jan) 19 3
- 18 Hook G M Progressive exophthalmos in toxic disease of thyroid gland review of recent literature with report of case of progressive post thyroidectomy proptosis in 6 year old Negro girl Arch Surg 48 214 221 (Mar) 1944
- 19 Lang B T Cause of exophthalmos West J Surg 39 602 609 (Aug) 1935
- 20 Loeb L and Friedman H Long continued injections of acid extract of anterior pituitary on thyroid gland and sex organs Proc Soc Exper Biol & Med 29 172 174 (Nov) 1931
- 21 Mann I Exophthalmic ophthalmoplegia and its relation to thyrotoxicosis Am J Ophth 29 654 673 (June) 1946
- 22 Marne D and Rosen S H Influence of gonads on exophthalmos in rabbits Proc Soc Exper Biol & Med 35 354 356 (Nov) 1936
- 23 — Exophthalmos in thyroidectomized guinea pigs by thyrotropic substance of anterior pituitary and mechanism involved Proc Soc Exper Biol & Med 30 901 903 (Apr) 1933
- 24 — Exophthalmos of Graves disease Its experimental production and significance Am J M Sc 188 565 571 (Oct) 1934
- 25 Marne D Spence A W and Cipra A Production of goiter and exophthalmos in rabbits by administration of cyanide Proc Soc Exper Biol & Med 29 832 835 (Apr) 1932
- 26 Means J H The nature of Graves disease with special reference to its ophthalmic component Am J M Sc 207 1 19 (Jan) 1944
- 27 Means J H Hertz M and Williams R H Graves disease with dissociation of thyrotoxicosis and ophthalmopathy Tr A Am Physic 66 61 4 (May) 1941
- 28 Means J H Hyperophthalmopathic Graves disease Ann Int Med 23 779 789 (Nov) 1945
- 29 Moore R F Exophthalmos and limitation of eye movements of Graves disease Lancet 2 51 (Oct) 1920
- 30 Mulvaney J H Exophthalmos of hyperthyroidism differentiation in mechanism pathology symptomatology and treatment of 2 varieties Am J Ophth 27 589 (June) 693 (July) 820 (Aug) 1944
- 31 Naffziger H C Progressive exophthalmos after thyroidectomy West J Surg 40 330-341 (Oct) 1932
- 32 — Progressive exophthalmos following thyroidectomy its pathology and treatment Tr Am S A 49 166 1 1931
- 33 — Pathologic changes in orbit in progressive exophthalmos with special reference to alterations in extra ocular muscles and optic disks Arch Ophth 9 1 2 (Jan) 1935
- 34 — Progressive exophthalmos following thyroidectomy its pathology and treatment Ann Surg 94 582 586 (Oct) 1931

- 35 — Exophthalmos Some principles of surgical management from neurosurgical aspect *Am J Surg* 75 25 41 (Jan) 1948
- 36 Paschkis K E and Cantarow, A Hyperophthalmic syndrome in thyroid disease *J Clin Endocrinol* 7 102 114 (Feb) 1947
- 37 Paulson D L Experimental exophthalmos and muscle degeneration induced by thyrotropic hormone *Proc Staff Meet Mayo Clin* 14 828 832 (Dec) 1939
- 38 — Experimental exophthalmos and muscle degeneration induced by the thyrotropic factor *Tr Am A Study Goiter* 1940 pp 309 311
- 39 Perkin H J and Lahey F H Exophthalmic goiter relation between blood iodine level and duration of symptoms in 305 cases *Arch Int Med* 51 875 879 (June) 1938
- 40 Pochin E E Exophthalmos in guinea pigs injected with pituitary extracts *Clin Sc* 5 75 91 (Aug) 1944
- 41 Poppen P C Personal communication
- 42 Poulton E P and Watt W L Treatment of exophthalmic goitre with deep x ray therapy *Lancet* 2 535 537 (Sept) 1934
- 43 — Treatment of exophthalmic goitre by deep x rays *Proc Roy Soc Med* 31 371 378 (Feb) 1938
- 44 Roberts E and Griffith J Q Quantitative study of cutaneous capillaries in hyperthyroidism *Am Heart J* 14 598 602 (Nov) 1937
- 45 Rundle F F and Pochin E F Orbital tissues in thyrotoxicosis quantitative analysis relating to exophthalmos *Clin Sc* 5 51 74 (Aug) 1944
- 46 Rundle F F and Wilson C W Bulging of eyelids with exophthalmos *Clin Sc* 5 31 49 (Aug) 1944
- 47 Salter W T and Soley M H Treatment of Graves disease with severe exophthalmos *M Clin North America* 28 484 498 (Mar) 1944
- 48 Schall L A and Reagan D J Malignant exophthalmos *Ann Otol Rhin & Laryng* 54 37 42 (Mar) 1945
- 49 Schockaert J A Enlargement and hyperplasia of thyroids in young duck from injection of anterior pituitary *Proc Soc Exper Biol & Med* 29 306 308 (Dec) 1931
- 50 Seed L Periodic paralysis in a patient with exophthalmic goiter controlled on 6 propylthiouracil *West J Surg* 55 640 646 (Dec) 1947
- 51 Smeher G A Reaction of orbital tissues in experimental exophthalmos following removal of Harders gland *Anat Rec* 85 240 259 (Mar) 1943
- 52 — Study of retrobulbar tissues in experimental exophthalmos in guinea pigs with reference to primary and secondary modifications *Am J Anat* 72 149 169 (Mar) 1943
- 53 — Histology of orbital and other fat tissue deposits in animals with experimentally produced exophthalmos *Am J Path* 15 341 351 (May) 1939
- 54 — Experimental production of exophthalmos resembling that found in Graves disease *Proc Soc Exper Biol & Med* 35 128 130 (Oct) 1936
- 55 — Comparative study of experimental and clinical exophthalmos *Am J Ophth* 20 1189 1203 (Dec) 1937
- 56 Soley M H Exophthalmos in patients with various types of goiter *Arch Int Med* 70 206 220 (Aug) 1942
- 57 Spaul E A Accelerated metamorphosis of frog tadpoles by injections of extract of anterior lobe pituitary gland and the administration of iodine *Brit J Exper Biol* 1 313 321 (Apr) 1924
- 58 — Experiments on the injection of pituitary body (anterior lobe) extracts to axolotls *Brit J Exper Biol* 2 33 55 (Oct) 1924
- 59 Thomson E S Orbital edema in exophthalmic goitre *Am J Ophth* 7 27 35 (Jan) 1924
- 60 White B V and Jones C M Rate of filtration through capillary walls as measured by pressure plethysmograph Observations on control subjects and on patients with intrahepatic disease thyrotoxicosis and myxedema *J Clin Investigation* 18 73 80 (Jan) 1939
- 61 Wilhams H H and Clute H M Thiouracil in treatment of thyrotoxicosis *JAMA* 128 65 69 (May) 1945



FIG 213 EXOPHTHALMIC SYNDROME WITHOUT HYPERTHYROIDISM

Chief complaints Gradual onset Nine months before admission bulging eyes and double vision which occurred in the morning at night and on looking to the extreme left Good appetite No weight loss

Left

Physical examination Age 30 Weight 102 lbs Exophthalmometer readings $\frac{23-26}{115}$ mm Exophthalmos on left greater than on right Thyroid normal

except for small adenoma of isthmus Pulse 84 BP 110/80

Laboratory data BMP plus 1% and minus 1%

Right

Treatment Desiccated thyroid 7 to 4 gr daily and 5 drops of Lugol's solution for 30 months when weight was 103 lbs Pulse 96 Double vision gone Exophthalmometer measurements gradually changed to $\frac{21-23}{115}$ mm

Patient tolerated treatment very well

Comment This is a comparatively mild degree of exophthalmos Treatment in this case was fairly satisfactory especially in regard to the double vision

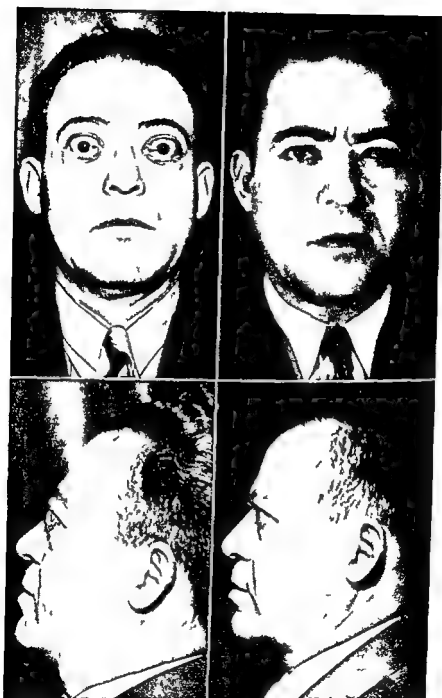


FIG 214 EXOPHTHALMOS Progressive exophthalmos after subtotal thyroidectomy for hyperthyroidism (Left top and bottom) Preoperative (Right top and bottom) After Naftziger's operation for decompression of orbits (Poppen J L Exophthalmos diagnosis and treatment of intractable cases *Am J Surg* 64 64-79)

SECTION 34

FACTITIOUS HYPERTHYROIDISM

SYNONYMS Self induced Alimentary, Thyrotoxicosis factitia

- I DEFINITION** Hyperthyroidism induced by surreptitious or known continuous administration of desiccated thyroid or thyroxine
- II APPEARANCE** Typical features found in hyperthyroidism
- III AGE** Adults
- IV SEX** Females usually
- V PHYSICAL STATUS**
- A GENERAL** Hyperthyroidism findings (see 26 VI)
- B EYES** Stare exophthalmos mild degrees
- C THYROID** Normal or slightly enlarged
- D HEART** Normal auricular fibrillation¹ flutter, congestive failure possible (see Figs 215 and 216)
- VI LABORATORY DATA**
- A URINE** Iodine increased (see Charts 76 and 77)^{6 10}
- B BLOOD CHEMICAL ANALYSES**
- 1 Cholesterol (plasma) Decreased⁶
- 7 Iodine Increased^{1 6 10}
- C BASAL METABOLIC RATE** Increased to various degrees up to 100 per cent (see Tables 38 and 39)

TABLE 38 BASAL METABOLIC RATE AND PLASMA CHOLESTEROL ON STOPPING INGESTION OF DESICCATED THYROID⁵

BMR	PLASMA CHOLESTEROL
+ 90%	112 mg %
+ 49 "	175 mg %
+ 10%	271 mg %

II RESPONSE TO INGESTION

- 1 Detectable clinical signs and symptoms may result from as little as 2 gr a day but from 80 to 100 gr per day were taken by one patient without untoward effects
- 2 Basal metabolic rate should rise from 30 to 50 per cent with from 11 to 12 gr taken per day

VII ETIOLOGY

- A REASONS FOR OVERDOSAGE**
- 1 Therapeutic reasons
 - 2 Error in prescription
 - 3 Unfamiliarity with dosage
 - 4 Surreptitious self administration for
 - a Relief of fatigue
 - b Weight reduction
 - c Deception

VIII PATHOLOGY

- A COMMENT**—No characteristic changes in thyroid of 2 cases studied (Dr Shields Warren)

IX PATHOLOGIC PHYSIOLOGY

- A THYROID GLAND**—Thyroid inhibition (either directly or through the pituitary) occurs with a subnormal metabolic rate following discontinuance of medication⁴

B CHOLESTEROL

- 1 Lowering of plasma cholesterol is proportional to elevation of basal metabolic rate
- 2 In myxedema, the drop in plasma cholesterol is far greater for a similar rise in basal metabolic rate (see Table 39)

C IODINE METABOLISM

- 1 Urinary excretion of iodine is
 - a Increased greatly
 - b Related to intake, approximately 50 micrograms in 24 hrs for each grain of desiccated thyroid
- 2 Organic or protein bound iodine is closely correlated to the rise in basal metabolic rate¹¹
- 3 Total blood iodine has a greater variation than protein bound depending on period of time after last dose, may reach 30 to 40 gamma per cent
- 4 Radioactive¹²
 - a Uptake decreased
 - b Urinary excretion increased

TABLE 39 · RELATIONSHIP BETWEEN CHOLESTEROL AND BASAL METABOLIC RATE ON ADMINISTRATION OF DESICCATED THYROID

CASE (ONE EACH)	DESICCATED THYROID	BMR	PLASMA CHOLESTEROL
Factitious hyperthyroidism	With	+ 90%	117 mg %
	Without	+ 10%	180 mg %
Myxedema	Without	- 30%	380 mg %
	With	- 5%	180 mg %

D WITHDRAWAL EFFECTS⁴

- 1 Basal metabolic rate falls
 - a Below normal, suggesting its inhibiting action on thyrotropic hormone, with gradual return to normal⁸
 - b Similar to that after
 - (1) Subtotal thyroidectomy
 - (2) Iodization
 - c More rapidly than following
 - (1) Antithyroid drugs
 - (2) Cessation of desiccated thyroid in cases of myxedema
- 2 Cholesterol rises above the normal level in some cases and is not evidence of previous thyroid deficiency
- 3 Persistence of hyperthyroidism on

stopping medication in some cases, indicates that desiccated thyroid produced hypersecretory diffuse hyperplastic goiter⁷

- E OTHER CHANGES**—Similar to noninduced hyperthyroidism probably (see 26 \I)

X SYMPTOMATOLOGY

- A HYPERTHYROIDISM**—Same complaints, see 26 \II

B HISTORY

- 1 Ingestion of desiccated thyroid may or may not be admitted
- 2 Same as hyperthyroidism—see 14 \III A 1 c

XI DIAGNOSIS**A SUMMARY**

- 1 Confession of surreptitious self administration of desiccated thyroid may not be obtained
 - a Various methods may have to be employed for detection
 - b Hospitalization (7 to 10 days) to watch patient carefully
- 2 Thyroid gland may be normal in size in spite of evident hyperthyroidism¹⁰
- 3 Laboratory data
 - a Iodine (urinary) excretion is often greater than that found in severe primary hyperthyroidism
 - b Cholesterol (plasma)
 - (1) Not diagnostic
 - (2) Proportionate to basal metabolic rate
 - c Basal metabolic rate falls rapidly after withdrawal of drug

XII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A GRAVES'S DISEASE** (see Figs 217 and 218)
- 1 Hypersecretory diffuse hyperplastic goiter⁷
 - 2 Elevated basal metabolic rate persists after discontinuing thyroid

B EXOPHTHALMOS**C CONGESTIVE HEART FAILURE****D ACUTE PSYCHOSIS¹³****E AMENORRHEA**

XIII TREATMENT

- A GENERAL—Desiccated thyroid discontinued
- B SURGICAL—Subtotal thyroidectomy may be necessary as hyperthyroidism may persist due to hypersecretory diffuse hyperplastic goiter initiated by desiccated thyroid^{7 10}

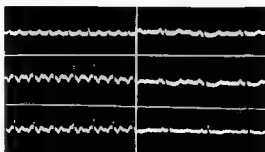
XIV PROGNOSIS

- A MAJORITY—Normal state without complications
- B MINORITY
- 1 Same course as in primary hyperthyroidism
 - 2 Persistence of hyperthyroidism
 - 3 Temporary myxedema (1 case)⁶

REFERENCES

- 1 Andersen W T Three cases of hyperthyroidism after weight reducing thyroidin treatment Acta med Scandinav 104 589 598 1940
- 2 Bruun E Exophthalmic goiter developing after treatment with thyroid preparations Acta med Scandinav 122 13 29 1945
- 3 Curtis E M and Cole V V The blood iodine in thyroid disease Tr Am A Study Goiter 1934 pp 142 155
- 4 Farquharson R F and Squires A H Inhibition of secretion of thyroid gland by continued ingestion of thyroid substance Tr A Am Physicians 56 87 97 1941
- 5 Hurxthal L M Unpublished data
- 6 — Experiences with use of desiccated thyroid methods of detecting self induced hyperthyroidism with report of case in which auricular fibrillation occurred New York State J Med 44 2217 2223 (Oct) 1944
- 7 — Exophthalmic goiter following the use of thyroid extract or diet for reduction of weight S Clin North America 11 441-443 (Apr) 1931
- 8 Loeser A Die schilddrusenwirksame Substanz des Hypophysenvorderlappens Arch f exper Path u Pharmacol 176 729 739 1934
- 9 Lous P Nine cases of Graves disease developed in connection with thyroid gland therapy Acta med Scandinav 122 81 94 1945
- 10 Perkins H J McFarland M H and Hurxthal L M Temporarily induced thyrotoxicosis from secretly ingested desiccated thyroid its detection by blood and urinary iodine estimations preliminary report Lahey Clin Bull 2 186 188 (Oct) 1941
- 11 Riggs D S Man E B and Winkler A W Serum iodine of euthyroid subjects treated with desiccated thyroid J Clin Investigation 24 777 781 (Sept) 1945
- 12 Skanse B N and Riggs D S Thyrotoxicosis factitia (alimentary thyrotoxicosis) its differentiation from spontaneous thyrotoxicosis with the aid of radioactive iodine J Clin Endocrinol 8 532 543 (July) 1948
- 13 Thompson G N Self induced psychosis with hyperthyroidism complicating manic depressive psychosis Experimental human hyperthyroidism Am J Psychiat 102 395 398 (Nov) 1945

FIG 215 FACTITIOUS HYPERTHYROIDISM (See also Fig 216) (Left) Auricular flutter in a patient with self induced hyperthyroidism After stopping thyroid flutter persisted (Right) Upon digitalization pulse became irregular (auricular fibrillation) and then reverted to normal rhythm (Hurxthal L M Experiences with the use of desiccated thyroid New York State J Med 44 2217 2223)



II CHOLESTEROL

- 1 Lowering of plasma cholesterol is proportional to elevation of basal metabolic rate
- 2 In myxedema, the drop in plasma cholesterol is far greater for a similar rise in basal metabolic rate (see Table 39)

C IODINE METABOLISM

- 1 Urinary excretion of iodine is
 - a Increased greatly
 - b Related to intake, approximately 50 micrograms in 24 hrs for each grain of desiccated thyroid
- 2 Organic or protein bound iodine is closely correlated to the rise in basal metabolic rate¹¹
- 3 Total blood iodine has a greater variation than protein bound depending on period of time after last dose, may reach 30 to 40 gamma per cent
- 4 Radioactive¹²
 - a Uptake decreased
 - b Urinary excretion increased

TABLE 39 RELATIONSHIP BETWEEN CHOLESTEROL AND BASAL METABOLIC RATE ON ADMINISTRATION OF DESICCATED THYROID

CASE (ONE EACH)	DESICCATED THYROID	BMR	PLASMA CHOLESTEROL
Factitious hyper thyroidism	With	+ 90%	112 mg %
	Without	+ 10%	180 mg %
Myxedema	Without	- 30%	380 mg %
	With	- 5%	180 mg %

D WITHDRAWAL EFFECTS⁴

- 1 Basal metabolic rate falls
 - a Below normal suggesting its inhibiting action on thyrotropic hormone with gradual return to normal¹⁸
 - b Similar to that after
 - (1) Subtotal thyroidectomy
 - (2) Iodinization
 - More rapidly than following
 - (1) Antithyroid drugs
 - (2) Cessation of desiccated thyroid in cases of myxedema
- 2 Cholesterol rises above the normal level in some cases and is not evidence of previous thyroid deficiency
- 3 Persistence of hyperthyroidism on

stopping medication in some cases, indicates that desiccated thyroid produced hypersecretory diffuse hyperplastic goiter^{2 7}

E OTHER CHANGES—Similar to noninduced hyperthyroidism probably (see 26 XI)**X SYMPTOMATOLOGY****A HYPERTHYROIDISM**—Same complaints see 26 XII**B HISTORY**

- 1 Ingestion of desiccated thyroid may or may not be admitted
- 2 Same as hyperthyroidism—see 14 XIII A 1 c

XI DIAGNOSIS**A SUMMARY**

- 1 Confession of surreptitious self administration of desiccated thyroid may not be obtained
 - a Various methods may have to be employed for detection
 - b Hospitalization (7 to 10 days) to watch patient carefully
- 2 Thyroid gland may be normal in size in spite of evident hyperthyroidism¹⁹
- 3 Laboratory data
 - a Iodine (urinary) excretion is often greater than that found in severe primary hyperthyroidism
 - b Cholesterol (plasma)
 - (1) Not diagnostic
 - (2) Proportionate to basal metabolic rate
 - c Basal metabolic rate falls rapidly after withdrawal of drug

XII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A GRAVES' DISEASE** (see Figs 217 and 218)
 - 1 Hypersecretory diffuse hyperplastic goiter^{2 7}
 - 2 Elevated basal metabolic rate persists after discontinuing thyroid

B EXOPHTHALMOS**C CONGESTIVE HEART FAILURE****D ACUTE PSYCHOSIS¹⁷****E AMENORRHEA**

XIII TREATMENT

- A GENERAL—Desiccated thyroid discontinued
- B SURGICAL—Subtotal thyroidectomy may be necessary as hyperthyroidism may persist due to hypersecretory diffuse hyperplastic goiter initiated by desiccated thyroid¹⁰

XIV PROGNOSIS

- A MAJORITY—Normal state without complications
- B MINORITY
- 1 Same course as in primary hyperthyroidism
 - 2 Persistence of hyperthyroidism⁷
 - 3 Temporary myxedema (1 case)⁵

REFERENCES

- 1 Andersen W T Three cases of hyperthyroidism after weight reducing thyroidin treatment *Acta med Scandinav* 104 589 598 1940
- 2 Bruun E Exophthalmic goiter developing after treatment with thyroid preparations *Acta med Scandinav* 122 11 29 1945
- 3 Curtis G M and Cole V V The blood iodine in thyroid disease *Tr Am A Study Goiter* 1934 pp 142 153
- 4 Farquharson R F., and Squires A H Inhibition of secretion of thyroid gland by continued ingestion of thyroid substance *Tr A Am Physicians* 56 87 97 1941
- 5 Hurxthal L M Unpublished data
- 6 — Experiences with use of desiccated thyroid methods of detecting self induced hyperthyroidism with report of case in which auricular fibrillation occurred, *New York State J Med*, 44 2217 2223 (Oct) 1944
- 7 — Exophthalmic goiter following the use of thyroid extract or diet for reduction of weight, *S Clin North America* 11 441-443 (Apr) 1931
- 8 Loever A. Die schilddrüsenwirksame Substanz des Hypophysenvorderlappens *Arch f exper Path u Pharmacol* 176 729 739 1934
- 9 Lous, P Nine cases of Graves disease developed in connection with thyroid gland therapy *Acta med Scandinav* 122 81 91 1945
- 10 Perlman H J, McFarland M D and Hurxthal L M Temporarily induced thyrotoxicosis from secretly ingested desiccated thyroid its detection by blood and urinary iodine estimations preliminary report *Lahay Clin Bull* 2 186-188 (Oct) 1941
- 11 Riggs D S., Man E B., and Winkler A W Serum iodine of euthyroid subjects treated with desiccated thyroid *J Clin Investigation* 24 722 731 (Sept) 1945
- 12 Skanse B N and Riggs D S Thyrotoxicosis factitia (alimentary thyrotoxicosis): its differentiation from spontaneous thyrotoxicosis with the aid of radioactive iodine *J Clin. Endocrinol* 8 532 543 (July) 1948
- 13 Thompson E N Self induced psychosis with hyperthyroidism complicating manic depressive psychosis Experimental human hyperthyroidism *Am J Psychiat* 102 395 398 (Nov) 1945

FIG 215 FACTITIOUS HYPERTHYROIDISM (See also Fig 216) (Left) Auricular flutter in a patient with self induced hyperthyroidism After stopping thyroid flutter persisted (Right) Upon digitalization pulse became irregular (auricular fibrillation) and then reverted to normal rhythm (Hurxthal L M Experiences with the use of desiccated thyroid, *New York State J Med*. 44 2217 2223)

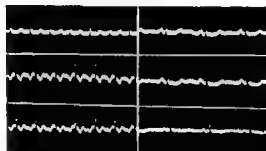




FIG 216 FACTITIOUS HYPERTHYROIDISM (See also Fig 215) Effect of factitious hyperthyroidism on the heart. Female age 53 who took 15 to 20 gr or more of desiccated thyroid daily. Note enlarged heart shadow on left probably due to auricular flutter. The picture on right is after cessation of self induced hyperthyroidism and return of normal rhythm (Hurxthal L M Experiences with the use of desiccated thyroid New York State J Med 442 2217 2223)

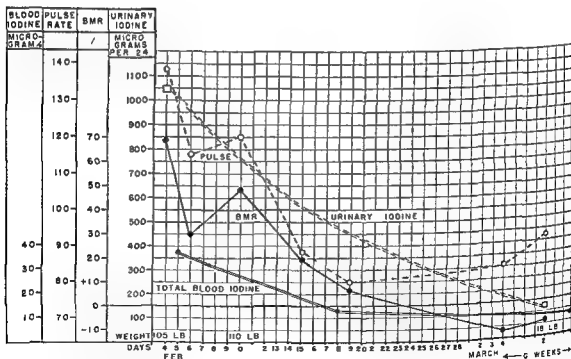


CHART 16 FACTITIOUS HYPERTHYROIDISM Observations on a patient who secretly took desiccated thyroid. Note urinary output of iodine (1050 micrograms/24 hrs) just before omission of thyroid. This quantity in 24 hrs is more than is excreted by a patient with severe hyperthyroidism and much less than a hyperthyroid patient on 10 to 50 drops of Lugol's solution daily (35 000 to 90 000 micrograms). Thus urinary iodine excretion is of diagnostic value. It should particularly be suspected when no enlargement of thyroid is found in a person who shows obvious clinical evidence of hyperthyroidism (Ierkin H J McFarland M D and Hurxthal L M). Temporarily induced thyrotoxicosis from secretly ingested thyroid: its detection by blood and urinary iodine estimations preliminary report Labey Clin Bull 2 186 188)

XIII TREATMENT

- A GENERAL—Desiccated thyroid discontinued
- B SURGICAL—Subtotal thyroidectomy may be necessary as hyperthyroidism may persist due to hypersecretory diffuse hyperplastic goiter initiated by desiccated thyroid^{7 10}

XIV PROGNOSIS

- A MAJORITY—Normal state without complications
- B MINORITY
- 1 Same course as in primary hyperthyroidism
 - 2 Persistence of hyperthyroidism
 - 3 Temporary myxedema (1 case)

REFERENCES

- 1 Andersen W T Three cases of hyperthyroidism after weight reducing thyroidin treatment *Acta med Scandinav* 104 589 598 1940
- 2 Bruun M Exophthalmic goiter developing after treatment with thyroid preparations *Acta med Scandinav* 122 13 29 1945
- 3 Curtis G M and Cole V V The blood iodine in thyroid disease *Tr Am A Study Goiter* 1934 pp 142 155
- 4 Farquharson R F and Squires A H Inhibition of secretion of thyroid gland by continued ingestion of thyroid substance *Tr A Am Physicians* 56 87 97 1941
- 5 Hurxthal L M Unpublished data
- 6 — Experiences with use of desiccated thyroid methods of detecting self induced hyperthyroidism with report of case in which auricular fibrillation occurred *New York State J Med* 44 2217 2223 (Oct) 1944
- 7 — Exophthalmic goiter following the use of thyroid extract or diet for reduction of weight *S Clin North America* 21 441-443 (Apr) 1931
- 8 Looser A Die schilddrüsenwirksamen Substanzen des Hypophysenvorderlappens *Arch f exper Path u Pharmacol* 176 729 739 1934
- 9 Lous P Nine cases of Graves disease developed in connection with thyroid gland therapy *Acta med Scandinav* 122 81 94 1945
- 10 Perkin H J McFarland M D and Hurxthal L M Temporarily induced thyrotoxicosis from secretly ingested desiccated thyroid its detection by blood and urinary iodine estimations preliminary report *Lahey Clin Bull* 2 186 188 (Oct) 1941
- 11 Riggs D S Man E B and Winkler A W Serum iodine of euthyroid subjects treated with desiccated thyroid *J Clin Investigation* 24 722 731 (Sept) 1945
- 12 Skanse B N and Riggs D S Thyrotoxicosis factitia (alimentary thyrotoxicosis) its differentiation from spontaneous thyrotoxicosis with the aid of radioactive iodine *J Clin Endocrinol* 8 532 543 (July) 1948
- 13 Thompson G N Self induced psychosis with hyperthyroidism complicating manic depressive psychosis *Experimental human hyperthyroidism Am J Psychiat* 102 395 398 (Nov) 1945

FIG 215 FACTITIOUS HYPERTHYROIDISM (See also Fig 216) (Left) Auricular flutter in a patient with self induced hyperthyroidism After stopping thyroid flutter persisted (Right) Upon digitalization pulse became irregular (auricular fibrillation) and then reverted to normal rhythm (Hurxthal L M Experiences with the use of desiccated thyroid *New York State J Med* 44 2217 2223)

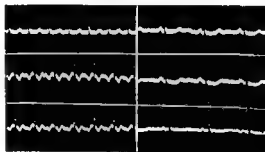




FIG 218 HYPOMETABOLISM PROBABLY THYROID DEFICIENCY AND DEVELOPMENT OF EXOPHTHALMOS ON DESICCATED THYROID

Chief complaints Swelling of face stiffness of joints and fatigue

History of present illness Nine months after a normal delivery patient gained 12 lbs Periods unchanged Developed sensitivity to cold Dry skin Somewhat forgetful and mentally slow

Left

Physical examination Age 28 Weight 149 lbs Pulse 56 BP 108/80 Some bloating of the face Dry skin Condition suggested a mild myxedema

Laboratory data Urine negative RBC 52 million Differential normal Total protein 7.9 Gm % Albumin 3.9 Gm % Globulin 3.5 Gm % Plasma cholesterol 174 mg % BMR minus 29%

Roentgenographic findings Skull normal

Treatment One gr desiccated thyroid (U S P) daily

Center

Progress

MONTHS

1½ Weight 149½ lbs Pulse 60 BMR plus 4% Marked improvement in all symptoms

8 Taking 1 gr of thyroid daily Weight 142 lbs Pulse 72 Total protein 6.1 Gm % Plasma cholesterol 120 mg % BMR plus 13% Patient noted left eye bulging Exophthalmometer reading right 16 mm left 19 mm Thyroid not palpably enlarged Thyroid medication discontinued

12 Weight 141 lbs Pulse 70 BMR plus 13% Exophthalmometer reading right 19 mm left 21 mm Noted palpitation warmth lacrimation Urinary iodine 995 micrograms/24 hrs Lugol's solution started

Right

MONTHS Weight 139 lbs BMR plus 14 12 and 8% (done elsewhere)

13 Exophthalmometer reading right 20 mm left 22 mm Propylthiouracil 300 mg a day

14 Weight 139½ lbs Pulse 72 BMR plus 1% Plasma cholesterol 133 mg % Exophthalmometer reading right 18 mm left 20 mm

30 Weight 135 lbs Pulse 100 Exophthalmometer reading right 21 mm left 22 mm Thyroid not enlarged Three months pregnant No treatment in past 16 months Feels fairly well

Comment At no time could a hyperplastic enlarged gland be felt The excretion of urinary iodine taken 16 days after discontinuing Lugol's solution was excessive and suggestive of factitious hyperthyroidism although this could not be proved The normal plasma cholesterol is not consistent but quite possible with myxedema The increase in total protein is characteristic



FIG 217 GRAVES'S DISEASE INDUCED BY TAKING DESICCATED THYROID Age 40 Mild exophthalmos following use of desiccated thyroid for obesity There was a slight enlargement of the thyroid gland and symptoms of hyperthyroidism which persisted 1 month after discontinuing thyroid Findings then Weight 164 lbs Pulse 88 Plasma cholesterol 1.6 mg % BMR plus 15% After 1 month on Lugol's solution weight 108 lbs Pulse 84 Plasma cholesterol 225 mg % BMR plus 2% One year later no iodine Weight 180 lbs Pulse 72 BMR minus 10% Exophthalmos persisted

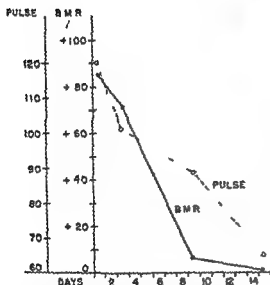


CHART 77 FACTITIOUS HYPERTHYROIDISM BMR and pulse rate in a person hospitalized for taking desiccated thyroid Note rapid fall The time taken for the BMR to return to normal after stopping desiccated thyroid is approximately the same following subtotal thyroidectomy or after iodine administration* (where a return to normal follows its use) However the drop is more precipitous in this case (Hurxthal L M Experiences with the use of desiccated thyroid New York State J Med 44 2217 2223)

* Means J H The Thyroid and Its Diseases Philadelphia Lippincott p 337

IX PATHOLOGY^{3 29 33 51}

A BENIGN TUMORS

1 Characteristics

- a Encapsulated mass
- b Clinically ranges from 2 to 10 cm in diameter
- Weight on removal between 25 and 200 Gm

2 Specific types

- a Embryonal adenoma
 - (1) Resembles embryonic thyroid tissue
 - (2) Cells are
 - (a) Moderate in size
 - (b) Polyhedral in shape
 - (c) Packed closely
 - (d) Arranged in
 - [1] Solid masses
 - [2] Strands
 - [3] Small clusters
 - (e) Embedded in fairly edematous fibrous tissue stroma
 - (3) Vascular supply
 - (a) Very abundant
 - (b) Thin walled vessels favor occurrence of
 - [1] Hemorrhages
 - [2] Cystic degeneration
 - (4) Extensive hemorrhage may cause a sharp increase in the size of the nodule
 - (5) Later there may be
 - (a) Fibrosis
 - (b) Calcification
- b Alveolar (fetal) adenoma (see Fig 221)
 - (1) Origin sometimes from fetal cell rests in intra acinar parenchyma
 - (2) Formation of small acini with very little colloid
 - (a) Clusters devoid of lumina (rare)
 - (b) Cell masses widely spaced
 - (c) Epithelium cuboidal
 - (3) Stroma edematous
 - (4) Changes which may take place
 - (a) Hemorrhage
 - (b) Cystic degeneration
 - (c) Fibrosis
 - (d) Calcification
 - (5) Blood vessels abundant

c Simple adenoma

- (1) Thyroid tissue fairly well differentiated
- (2) Epithelium with little evidence of functional activity
- (3) Hyperfunctioning solitary adenoma
 - (a) Epithelium high columnar
 - (b) Colloid present
 - (c) Remainder of thyroid normal
- (4) Hurthle cell adenoma (very rare type)^a
 - (a) Acini
 - [1] Small
 - [2] Colloid
 - [a] Scant
 - [b] Absent
 - (b) Cells
 - [1] Large
 - [2] Acidophilic
 - [3] Cytoplasm clear
 - [4] Nuclei slightly larger than normal

d Colloid adenoma

- (1) Follicles
 - (a) Huge
 - (b) Distended with colloid
 - (c) Papillary projections absent
 - (d) Scalloping of colloid not found
- (2) Epithelium
 - (a) Flat
 - (b) Low cuboidal
- (3) Stroma moderate amounts
- (4) Spontaneous hemorrhage frequent with sudden enlargement

e Papillary adenocystoma

- (1) Encapsulated mass
- (2) Papillae lined with tall columnar epithelium
- (3) Fluid within cyst may be
 - (a) Brownish
 - (b) Hemorrhagic
 - (c) Filled with small flecks of cholesterol
- (4) Follicles
 - (a) Well formed occasionally
 - (b) Scattered
 - (c) Scant in colloid
- (5) More apt to become malignant than other adenomas (see below)

SECTION 35

TUMORS OF THE THYROID

I DEFINITION	A neoplasm within the thyroid gland which may be benign or malignant, single or multiple discrete invasive or metastasizing usually associated with euthyroidism, but occasionally with hyperthyroidism or hypothyroidism	
II APPEARANCE	Not abnormal, 'goiter' or lumps in neck of various sizes rarely hyper or hypothyroid characteristics	
III AGE	Any, average around 45 years ^{20 23 25 6 31 47}	
IV SEX	Approximately 85 per cent females ^{11 23 31 47}	
V PHYSICAL STATUS		
A GENERAL	Euthyroidism usually, dysthyroidism rarely, about 5 per cent associated with hyperthyroidism, ³ or very rarely hypothyroidism	
B LARYNX (voice)	Normal or recurrent laryngeal paralysis, displacement of thyroid cartilage	
C NECK		
1 Thyroid	Localized discrete firm mass may be palpated in gland or multiple hard lumps beyond it, may be fixed to surrounding tissues (see Figs 219 220 and 224)	
2 Lymph glands	Normal or enlarged, especially above isthmus (Delphian gland ¹) if malignant tumor	
VI LABORATORY DATA		
A GENERAL (urine, hematology and blood chemical analyses)	Normal	
B IODINE	Variable	
C BASAL METABOLIC RATE	Normal	
VII ROENTGENOGRAPHIC FINDINGS		
A TRACHEA	Normal or may reveal displacement or compression	
B CHEST	Normal, intrathoracic extension or metastatic lesions	
C BONES	Normal or metastatic areas predominantly osteolytic ⁴²	
VIII ETIOLOGY		
A UNKNOWN		
B FETAL ANLAGE—Occurrence		
1 Nodular goiters—12 per cent		
2 Hyperplastic glands—8 per cent		
C PAPILLARY CYSTADENOMA—Origin and extension uncertain		
1 Thyroid to cervical lymph glands ⁷		
2 Aberrant thyroid tissue to thyroid gland (see Fig 232) ⁴⁸		
D COLLOID NODULES (see 17 VII)		

TABLE 40 KNOWN PRESENCE OF THYROID TUMOR PRIOR TO DIAGNOSIS²³

GROUP	HISTOLOGIC TYPE	YEARS (AVERAGE) OF EXISTENCE OF TUMOR BEFORE DIAGNOSIS
I	Fetal adenoma with invagination	108
	Papillary adenocystoma	4.5
II	Papillary adenocarcinoma	4.1
	Alveolar adenocarcinoma	3.2
III	Small-cell carcinoma	5.1
	Giant cell carcinoma	15.3

- [a] Small
- [b] Packed closely
- [2] Alveolar formation absent
- [3] Nuclei
 - [a] Prominent
 - [b] Hyperchromatic
 - [c] Filled with numerous mitotic figures
- [4] Invasion of
 - [a] Blood vessels
 - [b] Lymphatics
- (b) Diffuse type (diagnostic problem, for some feel it should be grouped with the lymphomas rather than the epithelial type)
 - [1] Cells
 - [a] Polyhedral
 - [b] Cytoplasm scant
 - [c] Pseudoalveolar groupings
 - [2] Mitotic figures vary
 - [3] Intimate relationship of stroma and tumor cells is most striking feature
- b Giant cell carcinoma (see Figs 230 and 231)
 - (1) Clinical course rapid
 - (2) From pre existing adenoma
 - (3) Characteristics
 - (a) Large
 - (b) Fleshy
 - (c) Very vascular type
 - (d) Fixation
 - (e) Infiltration
- (4) Microscopic
 - (a) Giant cells
 - [1] Numerous
 - [2] Variable
 - (b) Very vascular
 - (c) Necrosis
- 4 Miscellaneous types
 - a Epidermoid carcinoma (squamous cell)
 - (1) Origin from
 - (a) Thyroglossal duct
 - (b) Metaplasia of thyroid epithelium
 - (2) Description as for the other malignant tumors
 - (3) Microscopic
 - (a) Epithelial cells
 - [1] Numerous
 - [2] Clusters (pearl formation)
 - [3] Strands
 - (b) Keratinization in variable degrees
 - b Fibrosarcoma (rare)
 - (1) Gross appearance
 - (a) Gray pink
 - (b) Fleshy
 - (2) Microscopic—spindle cells arranged in strands
 - c Lymphoma
 - (1) Secondary to lymphomatous process elsewhere
 - (2) Pathologic changes as other lymphoid tumors
 - d Hurthle cell—same as adenoma, but with malignant features
 - Unclassified

TABLE 42 THYROID CANCER—AGE AND SEX DISTRIBUTION
(1928 to 1935 Inclusive)*

GROUP	HISTOLOGIC TYPE	PATIENTS			AGE (YEARS)	
		Females	Males	Total	Average	Range
I	Fetal adenoma with invasion	43	6	49	45.2	20-72
	Papillary adenocystoma	41	7	48	46.2	9-0
II	Papillary adenocarcinoma	33	5	38	44.8	13-80
	Alveolar adenocarcinoma	19	5	24	44.1	9-70
III	Small cell carcinoma	26	4	30	46.5	9-72
	Giant cell carcinoma	8	1	9	59.4	36-70
		170	28	198		

* See Table 45 for outcome

II MALIGNANT TUMORS

- 1 Adenomas with invasion (benign metastasizing—Group I)
 - a Histologic criteria for inclusion under malignancy are the invasion of
 - (1) Capsule
 - (2) Blood vessels
 - (3) Lymphatic channels
 - (4) Surrounding or distant tissues
 - b Types
 - (1) Alveolar adenoma (see Fig 222)
 - (2) Papillary adenocystoma (see Fig 223)
- 2 Adenocarcinoma (Group II)
 - a Origin
 - (1) Thyroid gland which has been normal
 - (2) Various adenomas frequently
 - b Characteristics
 - (1) Hard
 - (2) Asymmetrical
 - (3) Gradual increase in size of thyroid
 - (4) Fixed to surrounding structures
 - (5) Metastases to lymph nodes may be found
 - c. Microscopic
 - (1) Cellular anaplasia
 - (2) Mitotic figures
 - (3) Tumor giant cells are present
 - (4) Capsule absent

- (5) Invasion of
 - (a) Surrounding structures
 - (b) Blood vessels
 - (c) Lymph glands
- d Types
 - (1) Papillary (see Figs 224 227)
 - (a) More anaplasia than alveolar
 - (b) Solid clusters of tumor cells
 - (2) Alveolar (see Fig 228)
 - (a) Acinar formation may be marked
 - (b) Follicles have little colloid
 - (c) Normal thyroid architecture with only slight maintenance of alveolar form may be seen
- 3 Carcinoma simplex (Group III)
 - a Small cell carcinoma (see Fig 229)
 - (1) Types
 - (a) Compact—may or may not originate from pre existing adenoma
 - (b) Diffuse—practically never arises from former adenoma
 - (2) Characteristics are the same as for other malignant growths
 - (3) Microscopic
 - (a) Compact
 - [1] Cells

TABLE 41 TYPES OF THYROID MALIGNANCY (1928 1947 Inclusive)

GROUP	HISTOLOGIC TYPE	INDIVIDUAL NUMBER	TOTAL NUMBER	PER CENT
I	Adenoma with invasion of		108	24.6
	Blood vessel	12		
	Capsule and lymphatics	61		
	Capsule or lymphatic and blood vessels	35		
II	Adenocarcinomas		203	46.2
	Papillary	154		
	Alveolar	49		
III	Carcinoma simplex		108	24.6
	Small cell	72		
	Giant cell	36		
IV	Miscellaneous		20	4.6
	Hurthle cell	7		
	Fibrosarcoma	7		
	Lymphoma	3		
	Epidermoid	2		
	Unclassified	1		
Grand total			439	

- (3) Deep in neck as carotid body tumor
 - (4) Behind thyroid
 - Other facts
 - (1) Unilateral
 - (2) Superficial
 - (3) Movable
 - (4) Mass may exist for years as enlarged lymph gland or glands
 - 2 Incidence
 - a Approximately 0.2 per cent of goiter cases
 - b Majority are malignant⁴⁵
 - 3 Origin
 - a Ultimobranchial bodies — present trend opposes this view
 - b Extension of
 - (1) Papillary cystadenoma of thyroid⁴¹
 - (2) Other thyroid malignancies, especially papillary carcinoma⁴²
 - 4 Pathology—usually papilliferous type
 - 5 Treatment—surgical removal to determine malignancy and hemithyroidectomy (see 35 XIV C)
- C THYROGLOSSAL CYST OR FISTULA⁸**
- 1 Description (see Figs 233 and 234)
 - a Outline
 - (1) Oval
 - (2) Round
 - b Consistency
 - (1) Elastic
 - (2) Fluctuating
 - Size is
 - (1) Variable
 - (2) Increased gradually
 - d Locations
 - (1) In front of thyrohyoid membrane
 - (2) Midline or to left of midline
 - Other data
 - (1) Superficial
 - (2) Immobile but moves with swallowing
 - (3) Firmly attached to hyoid bone
 - (4) Inflammation may develop suddenly
 - (5) Rupture is possible
 - (6) Any age group susceptible
 - 2 Incidence
 - a About 1 in 50 of surgical diseases of the thyroid
 - b One in approximately 500 goiter patients
 - 3 Etiology
 - a Failure of the thyroglossal duct to disappear
 - b Fistula
 - (1) Passes usually from foramen cecum down to the thyroid isthmus
 - (2) Is attached to hyoid bone in many cases
 - (3) May be result of
 - (a) Ruptured cyst
 - (b) Incision
 - 4 Pathology
 - a Wall of cyst may be thick
 - b Epithelium
 - (1) Cylindrical
 - (2) Ciliated
 - c Cyst contents
 - (1) Cholestrin
 - (2) Viscid material
 - (3) Purulent if inflammation is present
 - d Osteomyelitis of hyoid bone may develop (rare)
 - 5 Symptomatology
 - a None, except for cosmetic complaint
 - b Onset at puberty
 - c Localized pain if inflamed
 - 6 Treatment—every part of entire tract or cyst must be excised completely or else condition may recur
 - a Section of hyoid bone should be removed
 - b Tract is followed to base of tongue
- D BRANCHIAL CYST AND SINUS**
- 1 Description
 - Outline
 - (1) Round
 - (2) Smooth
 - (3) Unilocular
 - b Consistency
 - (1) Fluctuant
 - (2) Soft
 - c Size—about hen's egg or smaller
 - d Location—swelling behind or below angle of the jaw
 - Other facts
 - (1) Superficial
 - (2) Bulge outward as they enlarge
 - (3) Abscess may form
 - (4) Rupture occasionally

X SYMPTOMATOLOGY

A BENIGN TUMORS

- 1 None except when large enough to produce pressure
- 2 Hemorrhage may occur with acute pressure symptoms

B MALIGNANT TUMORS

- 1 None sometimes for years
- 2 The following may develop
 - a Hoarseness
 - b Dysphagia
 - c Dyspnea
 - d Stridor
 - e Edema of face
 - f Venous congestion of neck veins
 - g Metastatic lesions causing
 - (1) Bone pain
 - (2) Fractures

C THYROID FUNCTION

- 1 Euthyroidism usual
- 2 Hypothyroidism occasionally
- 3 Hyperthyroidism rare

TABLE 43 INCIDENCE OF MALIGNANCY IN SOLITARY OR MULTIPLE NODULAR OR OTHER GOITERS

TYPE OF GOITER	PER CENT MALIGNANT
Clinically presumed solitary nodules ^{10 16 20}	10.8-24.5
Suspected nonfunctioning nodule by radioactive iodine technic (Dobyns) ^{7 13}	18
Surgically verified solitary nodules (estimated) ^{10 20 34}	18
Multiple nodules ^{4 11 4 43}	0.5-1.1
Hyperplastic goiter ^{11 45 47}	<1
All goiters (surgical) ^{4 11 5 43 47}	2.5-3
Incidence in relation to malignancy of other organs ^{8 9 30}	1-3

XI DIAGNOSIS

A HISTORY

- 1 Unreliable, unless rapid growth
- 2 Duration of neoplasm is not important (see Table 40)
- 3 Recent onset of symptoms is suggestive

B CHARACTERISTICS

- 1 Localized, discrete, firm tumor
- 2 Fixation to surrounding structures
- 3 Multiple, hard lumps beyond thyroid gland
- 4 Cervical lymph gland involvement
- 5 Delphian gland enlargement believed to be helpful¹
- 6 Recurrent laryngeal paralysis
- 7 Less radioactive emanation from nodule than surrounding tissue¹
- 8 Exclusion of other lesions (see below)
- 9 Roentgenographic evidence of metastases
- 10 Histologic studies are essential for (except in obvious and hopeless malignancy)
 - a Diagnosis
 - b Proper therapy

XII DIFFERENTIAL DIAGNOSIS²

A THYROIDITIS—see 19 XI 21 XI 22 XI

B LATERAL APERTANT THYROID TUMOR

1 Description

- a Outline discrete sometimes bilateral
- b Consistency
 - (1) Firm
 - (2) Soft
- c Size—variable usually small gland like structures
- d Locations
 - (1) In front of sternomastoid muscle
 - (2) Close to internal jugular vein

TABLE 44 DISTRIBUTION OF KNOWN METASTASES²³

	NECK	LUNGS	MEDIASTINUM	BONE	SOFT TISSUES	VISCERAL
Papillary adenocystoma	7	2		1		1
Papillary adenocarcinoma	2	2	1			1
Alveolar adenocarcinoma	4	3	1			1
Small-cell carcinoma	6	5		2	2	
Giant-cell carcinoma	2	2	2	1		
Total	21	14	4	4	2	3

- (3) Sublingual—beneath the tongue
- e Other data
 - (1) Immobile
 - (2) Very vascular mucous membrane congested over it
 - (3) Pedunculated occasionally
 - (4) Laryngoscopic examination is sometimes necessary for diagnosis
- 2 Incidence
 - a Data—approximately 1 in every 5,000 to 10,000 cases of thyroid disease
 - b Sex—females affected more often than males
- 3 Etiology—the thyroid gland fails to descend into its normal position
- 4 Pathology
 - a Colloid goiter which may develop
 - (1) Cystic degeneration
 - (2) Hemorrhage
 - b Hyperplastic goiter
 - c Malignancy
- 5 Symptomatology
 - a Onset
 - (1) At birth
 - (2) During puberty
 - (3) Insidious
 - b Fullness in throat
 - c Speech impairment
 - d Hemoptysis with ulceration of mucous membranes
 - Thyrotoxicosis, rarely
 - f Sudden increase in size due to hemorrhage
 - g Large goiter may produce
 - (1) Cough
 - (2) Dyspnea
 - (3) Dysphagia
- 6 Treatment—removal of goiter, only if
 - a Tumor interferes with swallowing
 - b Hemorrhage occurs
- 7 Result—myxedema develops postoperatively
- I INFLAMMATORY GLANDS
 - 1 They are related to adjacent focus of infection
 - 2 Recent origin can be confirmed
- J GUMMATOUS LYMPH NODES OF SYPHILIS
 - 1 Rare
 - 2 Serologic tests are positive
- K TUBERCULOUS CERVICAL ADENITIS
 - 1 Tuberculosis may be present elsewhere
 - 2 Multiple involvement of cervical glands
- 3 Early stage
 - a Firm
 - b Round
 - c Small
 - d Isolated
 - e Painless
 - f Movable
- 4 Later stage
 - a Fused
 - b Irregular
 - c Adherent
 - d Tender
 - e Overlying skin may be red
 - f Caseation may form
 - g Calcification (demonstrated by roentgenograms)
- 5 Microscopic section for definite diagnosis
- L HODGKIN'S DISEASE (including lymphosarcoma, lymphoblastoma—see Fig 236)
 - 1 Lymph glands
 - a Noninflammatory
 - b Grapelike, may become quite large
 - c Movable early, later fixed
 - d Necrosis absent
 - e Majority involved
 - 2 Pel Epstein fever in some cases
 - 3 Diagnosis by biopsy
- M LYMPHATIC LEUKEMIA
 - 1 Acute
 - a Youthful person
 - b Nodes
 - (1) Growth rapid
 - (2) Multiple involvement
 - c Tonsils enlarged
 - d Hemorrhages are subcutaneous
 - e Blood picture typical
 - 2 Chronic
 - Lymph nodes
 - (1) Enlarged
 - (2) Indurated
 - (3) Generalized
 - b Blood picture diagnostic
 - Debility
- N PARATHYROID ADENOMA—see 38
- O NEUROFIBROMA
 - 1 Origin anywhere in nerve tissue
 - 2 Positive diagnosis by biopsy
- P CAROTID BODY TUMOR
 - 1 Mass ■ located at the notch made by the division of the common carotid into its external and internal branches

- (5) Grow slowly
- (6) Movable, but only moderately
- (7) History of recurrent swelling and soreness sometimes with internal discharge (see branchial sinus below)
- 2 Incidence
 - a About 1 in 200 cases of surgical disease of the thyroid
 - b Sex—males more often affected
- 3 Etiology
 - a Second branchial cleft, rarely the first, fails to become obliterated with the formation of the cyst
 - b Branchial sinus
 - (1) Empties into pharynx close to tonsil
 - (2) Descends beneath diaphragm muscle
- 4 Pathology
 - a Epithelial lining
 - (1) Squamous stratified
 - (2) Columnar
 - (3) Ciliated
 - b Wall contains lymphoid tissue
 - c Cyst contents
 - (1) Fluid
 - (a) Colorless
 - (b) Thin
 - (c) Viscid
 - (d) Opaque
 - (2) Fatty debris
 - (3) Cholesterol
 - (4) Epithelial cells
 - d Epithelium may develop (unusual)
- 5 Symptomatology
 - a Progressive painless swelling under angle of jaw
 - b Sinus
 - (1) Discharge escapes through a dimple in front of sternomastoid muscle
 - (2) Dimple moves with swallowing
 - (3) Exit of tract shows flecks of pigmentation on the skin
- 6 Treatment
 - a Excision of entire cyst
 - b The following should be avoided because they re-establish the fistula or fluid
 - (1) Drainage
 - (2) Curettage
 - (3) Caustics

III LARYNGOCELE (rare)

- 1 Characteristics
 - a Round mass opposite or above level of larynx
 - b Unilateral
 - c Enlargement on swallowing or holding breath
 - d Air may be demonstrated in it by fluoroscopic examination
- 2 Symptomatology
 - a None usually
 - b Hoarseness
- F METASTATIC NODULES IN THYROID OR NECK GLANDS¹
 - 1 Origin
 - a Stomach
 - b Lungs
 - c Lips
 - d Tonsils
 - e Pharynx
 - f Larynx
 - 2 Early—glands are
 - a Single
 - b Movable
 - c Small
 - d Hard
 - 3 Later—glands are
 - a Large
 - b Fixed
 - c Widespread
- G PRIMARY CARCINOMAS
 - 1 Origin
 - a Branchial remnants
 - b Parathyroids
 - 2 Incidence—very rare
- H LINGUAL GOITER (see Fig 235)
 - 1 Description
 - a Outline
 - (1) Surface smooth
 - (2) Irregular if cysts or colloid nodules are present
 - (3) Round
 - (4) Lobulated
 - b Consistency
 - (1) Hard
 - (2) Soft
 - (3) Cystic
 - c Size—cherry to egg
 - d Locations
 - (1) Supralingual—on tongue
 - (2) Intra lingual—within substance of posterior third of tongue

- (2) Entire tumor bed must be exposed to radiation, but normal tissue should be protected because of the following changes from heavy radiation
 - (a) Telangiectasia of the skin
 - (b) Soft tissue induration
 - (c) Certain degree of fixation of the neck, if portals are large enough to produce muscle fibrosis
 - (3) Dosage must be sufficient to destroy the tumor tissue completely
 - (a) Lethal dosage has been established in certain tumors
 - (b) In alveolar adenocarcinoma, the dosage required for its destruction is so great that it is not advisable to treat a large field because of the damage to surrounding normal tissues
 - (c) The probable cause of failure in lesions other than alveolar adenocarcinoma, is the presence of metastases outside of the treated area
 - (d) Tumor may frequently return in an area after treatment with the estimated lethal dose
- b Procedure**
- (1) Cross fire method is preferable
 - (2) One treatment is given daily
 - (3) Three portals are used
 - (a) One portal on each side of the neck and the third in the midline
 - [1] Care should be taken *not to overlap the fields*
 - [2] Greatest percentage should enter the tumor bed
 - (b) The size of the portal depends on the
 - [1] Proportions of the original growth
 - [2] Degree of substernal extension
- c Dosage**
- (1) Total amount of 6 000 mmeasured in air are delivered to the skin during one series of treatment
 - (a) A total of 2 000 m is given through each portal
 - (b) Each portal is treated daily after the first three treatments, using 150 r to each (a total of 450 r daily)
 - (c) If the patient is debilitated it is necessary to decrease the dose to 100 r to each portal daily
 - (2) Total depth dosage—6 000 r given externally provides a dose of approximately 4 800 r, 2 cm beneath the skin
 - (3) The following factors are used
 - (a) K. V P 200, milliamperes 20, 24 r units/min
 - (b) Filter 2 mm copper, 1 mm of aluminum added
 - (c) Distance 50 cm, portal 7 to 10 sq cm, half value layer 13
 - (4) Treatments carried out daily, except Sunday, unless complications occur
- d Complications**
- (1) Radiation sickness
 - (a) Frequent complaint when large amounts are delivered
 - (b) Symptomatology
 - [1] Nausea
 - [2] Vomiting
 - [3] Irritability
 - [4] Restlessness
 - (c) Management
 - [1] Daily dose decreased
 - [2] Cortisone orally
 - (d) This is not serious usually ceases within 72 hrs
 - (2) Dermatitis
 - (a) Development in some cases has been observed about 7 to 10 days after irradiation
 - (b) Quite severe occasionally
 - (c) Six to 8 weeks may be required to heal entirely
 - (3) Laryngitis—disappears in 9 to 10 weeks time
 - (4) Tracheitis—recovery in 9 to 10 weeks

- 2 It enlarges upward and inward toward the pharynx

Q DEEP CERVICAL ABSCESS

- 1 Characteristics
 - a Inflammatory exudate is found beneath the deep cervical fascia
 - b Infected areas are within the region from which they drain
 - c Stonelike
 - Large
 - Fixed
 - f Firm
 - g Brawny edema
 - h Superficial redness
- 2 Symptomatology
 - a Local soreness
 - b Painful swallowing
 - Difficulty breathing due to edema of larynx
 - d Fever

XIII. COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A GENERAL

- 1 Metastases
 - a Cervical lymph nodes
 - b Lungs
 - c Bones (see Fig 237)
 - d Other areas
- 2 Hemorrhage
- 3 Tracheal compression
- 4 Laryngeal nerve may be affected
- 5 Inanition

XIV TREATMENT

A INTRODUCTION—Surgery ■ indicated for all tumors (benign and malignant) after careful assessment of probable

- 1 Chance of malignancy
 - a Actual
 - b Potential
- 2 Risk
- 3 Duration of life in presence of advanced age and/or some other incurable disease

■ BENIGN TUMORS—Operative procedure⁹

- 1 Anesthesia—cyclopropane oxygen
- 2 Curved collar incision, which ■ higher on side of goiter
- 3 Fat and platysma divided
- 4 Deep cervical fascia incised

- 5 Sternocleidomastoid muscle freed
- 6 Median incision of deep cervical fascia
- 7 Division of prethyroid muscles on involved side
- 8 Elevation and medial retraction of adenoma
- 9 Division of middle thyroid veins
- 10 Lateral dissection
- 11 Ligation of inferior thyroid artery in continuity
- 12 Exposure of
 - a Recurrent nerve
 - b Inferior parathyroid
- 13 Application of clamps to superior and inferior portions of lobe containing adenoma
- 14 Excision of adenoma leaving a thin shell of normal thyroid tissue
- 15 Reconstruction of remnant
- 16 Prethyroid muscles sutured
- 17 Closure of skin and platysma with clips
- 18 Drain is used only if there is a large dead space

C MALIGNANT TUMOR⁷

- 1 Surgical
 - a Adenoma with blood vessel invasion only—simple excision
 - b Adenoma with capsule or lymph gland invasion
 - (1) Radical neck dissection of lymph nodes on affected side
 - (2) Hemithyroidectomy
 - (3) Roentgen therapy (postoperative)
 - c Carcinoma (Grade II) with capsule invasion—as above, including removal of
 - (1) Internal jugular vein
 - (2) Sternocleidomastoid muscle
 - d Carcinoma (Grade III)
 - (1) Extensive removal
 - (2) Detachment of carcinomatous tissue from trachea
 - (3) Tracheotomy to prevent compression during roentgen therapy
- 2 Postoperative roentgen therapy^{1 17 21}
 - a Comment
 - (1) Radiation therapy ■ advisable immediately after recovery from the operation

- (b) Administration of radioactive iodine as above
- (c) Time and frequency of dosage individualized
- f Complications⁴⁶
 - (1) Acute hyperthyroidism (within 2 weeks)
 - (2) Spinal fluid pressure may increase
 - (3) Amenorrhea
 - (4) Blood dyscrasia with a decrease in
 - (a) Red blood count
 - (b) Hemoglobin
 - (c) Lymphocytes
 - (d) Platelets
 - (5) Myxedema
- g Results^{41, 46}
 - (1) Estimated 40 to 50 per cent receive considerable benefit, justifying the therapy
 - (2) Under 25 per cent are greatly improved, and life is prolonged
 - (3) Cures yet to be established

XV PROGNOSIS^{79, 83}

A BENIGN TUMORS

- 1 Excellent
- 2 Metastases have been known to occur from histologically benign lesions

II MALIGNANT TUMORS

- 1 Groups I and II comprise 80 per cent of total
 - a Surgery without roentgen therapy—data inconclusive
 - b Surgery followed by roentgen therapy—results favorable
- 2 Group III
 - a Surgery alone—short lived
 - b Surgery and roentgen therapy—one third that of Groups I and II
- 3 Miscellaneous types
 - a Variable
 - b Similar to Group III

XVI CAUSES OF DEATH

A METASTASES

B CACHEXIA

REFERENCES

- 1 Berard L, Dargent M and Gurnet P Factors in prognosis of thyroid Principles of treatment based on 210 cases J internat chir 8 601 655 (Mar Apr) 1948
- 2 Black B M Papillary adenocarcinoma of the thyroid gland so called lateral aberrant thyroid tumors West J Surg 56 127 144 (Mar) 1948
- 3 Boyd W Textbook of Pathology ed 4 Philadelphia Lea & Febiger 1943 pp 744 749
- 4 Brenizer H G and McKnight R II True adenomas of thyroid gland and their relation to cancer Tr Am A Study Gouter 1940 pp 176 190
- 5 Cattell R II Tumors of lateral aberrant thyroid origin Tr Am A Study Gouter 1940 pp 218 221
- 6 — A more optimistic approach to cancer of the thyroid West J Surg 54 444 449 (Nov) 1946
- 7 — Personal communication
- 8 Clute H M and Cattell R B Thyroglossal Duct Diseases The Cyclopedia of Medicine and Surgery and Specialties vol 15 Philadelphia Davis 1946 p 55
- 9 Clute H M and Smith L W Cancer of thyroid gland Arch Surg 118 1 20 (Jan) 1929
- 10 Cole W H Majarakas J D and Slaughter D P Incidence of carcinoma of the thyroid in nodular goiter J Clin Endocrinol 9 1007 1011 (Oct) 1949
- 11 Cole W H Slaughter D P and Rossiter L J Potential dangers of nontoxic nodular goiter JAMA 127 883 885 (Apr) 1945
- 12 Cope O Dobyns B M Hamlin E Jr and Hopkirk J What thyroid nodules are to be feared? J Clin Endocrinol 9 1012 102 (Oct) 1949
- 13 Dobyns B M Skanse B and Malool F A method for the preoperative estimation of function in thyroid tumors its significance in diagnosis and treatment J Clin Endocrinol 9 1171 1184 (Nov) 1949
- 14 Fitzgerald P J and Foote F W Jr The function of various types of thyroid carcinoma as revealed by the radioautographic demonstration of radioactive iodine (131) J Clin Endocrinol 9 1153 1170 (Nov) 1949
- 15 Frantz V K Ball R P, Keston A S and Palmer W W Thyroid carcinoma with metastases studied with radioactive iodine Ann Surg 119 668 669 (May) 1944
- 16 Goldman Leon Experiences with thyroidectomy in a thyroid clinic J Clin Endocrinol 8 781 788 (Sept) 1948
- 17 Haagensen C D Cancer of thyroid its radio sensitivity Am J Cancer (Suppl) 15 063 2105 (July) 1931
- 18 Hamilton J G The use of radioactive tracers in biology and medicine Radiology 39 541 572 (Nov) 1942
- 19 Hamilton J G Soley M H and Eschom K II Deposition of radioactive iodine in human thyroid tissue Univ California Publ Pharmacol 1 339 358 1940
- 20 Hare H F Cancer of thyroid in children Radiology 21 131 143 (Feb) 1937
- 21 — Radiation treatment of carcinoma of thyroid Am J Roentgenol 46 451 453 (Oct) 1941

TABLE 45 THYROID CANCER—SURVIVAL AFTER TREATMENT
TOTAL 198 PATIENTS²³

GROUP	HISTOLOGIC TYPE	TOTAL NO		5 YEARS		10 YEARS		15 YEARS		20 YEARS	
		OF		NO	PER CENT	NO	PER CENT	NO	PER CENT	NO	PER CENT
		PATIENTS									
I	Fetal adenoma with inva sion	49	38	77.5	19	38.7	7	14.2	5	10.1	
	Papillary adenocystoma	48	31	64.5	23	47.9	13	27.0	2	4.1	
II	Papillary adenocarcinoma	39	30	76.9	20	52.6	7	18.4	4	10.5	
	Alveolar adenocarcinoma	24	7	29.1	5	20.8	1	4.1	0		
III	Giant cell carcinoma	9	2	22.2	1	11.1	0		0		
	Small cell carcinoma	30	6	20.2	2	6.6	0		0		

(5) Difficulty in swallowing—hospitalization may be necessary

(6) Sloughing of tissues—rare

(7) Myxedema

(8) Anemia

■ Management

(1) Reassurance

(2) Inform patient regarding possibility of

(a) Sore throat

(b) Blistering of the skin

3 Thiouracil—will readily suppress hormone production by functioning metastases from thyroid adenocarcinoma

D THYROID METASTASES (pulmonary and osseous)

1 Roentgen therapy²⁴

a Indications

(1) Pain

(2) Limited number of metastases

(3) Evidence of growth as noted by repeated observation some remain stationary for years especially in the lungs

(4) Radiosensitivity as determined by biopsy especially

(a) Papillary adenocarcinoma

(b) Small-cell carcinoma

(c) Benign metastasizing tumor

b Dosage—as for neck except when metastases in

(1) Liver

(2) Retroperitoneal region

■ Results

(1) No statistical data

(2) Favorable in Groups I and II because

(a) Condition is quite stationary

(b) Roentgen therapy is very effective

2 Radioactive iodine therapy (see 26 \VI H)¹⁵ ■ ■ ■ ■ ■ ■ ■ ■ ■ ■

a This mode of treatment is still in its experimental stages but indications are the same as for roentgen therapy

b Isotopes are taken up infrequently by metastatic areas which can be demonstrated by

(1) Geiger Muller apparatus

(2) Radiosutographic determinations²¹

c Radioactive material is linked with the structural qualities of the tumor, especially as to

(1) Follicular pattern

(2) Presence of colloidlike material

d Although over 50 per cent of metastatic lesions take up radioactive iodine as shown by radiosutographs of biopsied tissue (Groups I and II), very few accumulate enough to warrant radioactive iodine therapy without inducing greater avidity¹⁴ ⁴⁶

e Dosage

(1) Functional metastases (rare) by radioactive iodine alone¹¹ ■ ■

(a) Single dose of I¹³¹ about 50 to 150 microcuries

(b) Cumulative dosage about 150 to 900 microcuries

(2) Nonfunctional metastases

(a) Methods to increase iodine uptake by tumor⁴¹ ⁴⁶

[1] Total thyroidectomy

[2] Injection of thyrotropic hormone

[3] Thiouracil ingestion



FIG 219 CARCINOMA OF THYROID Age 60 Lump in throat for 12 years Loss of 20 lbs in 6 months Cough



FIG 220 CANCER OF THYROID Inoperable Compare with Figure 236 showing similar growth due to lymphosarcoma



FIG 221 FETAL ADENOMA Irregular colloid deposits follicles and fetal cell masses separated Struma edematous and vascular Little scarring Low power (x 28)

- 22 — Personal communication
- 23 Hare H F and Salzman F A Cancer of the thyroid ten to twenty year follow up *Am J Roentgenol* 63 881 888 (June) 1950
- 24 Hinton J W, and Lord J W., Jr Is surgery indicated in all cases of nodular goiter toxic and nontoxic? *J.A.M.A.* 129 600 606 (Oct) 1945
- 25 Horn R. C., Welty R F., Brooks F P., Rhoads J E and Pendergrass E P Carcinoma of thyroid *Ann Surg* 126 140 155 (Aug) 1947
- 26 Kennedy R L J Nodular goiter among in infants and children *Tr Am A Study Goiter* 1940 pp 322-326
- 27 Keston A S Ball R P., Frantz V K., and Palmer W W Storage of radioactive iodine in a metastasis from thyroid carcinoma *Science* 65 362 363 (Apr) 1947
- 28 Lahey F H Tumors of neck *S Clin North America* 27 486 501 (June) 1947
- 29 Lahey F H Hare H F., and Warren S Carcinoma of thyroid *Ann Surg* 112 977 1005 (Dec) 1940
- 30 Leiter L Seidlin S M Mannelli L D and Baumann E J Adenocarcinoma of the thyroid and hyperthyroidism and functional metastases I Studies with thiouracil and radioactive iodine *J Clin Endocrinol* 6 247 261 (Mar) 1946
- 31 Marinelli L D Foote F W., Hill R F and Hooker A F Retention of radioactive iodine in thyroid carcinomas *Am J Roentgenol* 58 17 33 (July) 1947
- 32 Martin J D Jr and Etkin D C Hurthle cell tumors of thyroid *Ann Surg* 170 169 176 (Aug) 1939
- 33 McClintock J C., Kinck G H and Conrad J E Cancer of the thyroid gland *Tr Am A Study Goiter* 1940 pp 161 169
- 34 Meissner W A Personal communication
- 35 Meissner W A and Lahey F H Cancer of the thyroid in a thyroid clinic, *J Clin Endocrinol* 8 749 761 (Sept) 1948
- 36 Pemberton J deJ Malignant lesions of thyroid gland review of 774 cases *Surg Gynec & Obst* 59 417-430 (Oct) 1934
- 37 Pemberton J deJ and Lovelace W R., Jr Malignant lesions of thyroid gland *S Clin North America* 21 1037 1062 (Aug) 1941
- 38 Portmann U V Malignant tumors of thyroid gland report of 200 consecutive cases *Surg Gynec & Obst* 70 185 192 (Feb) 1940
- 39 Rosh R., and Raider L Radiation therapy of carcinoma of thyroid *Radiology* 44 556 564 (June) 1945
- 40 Seidlin S M Mannelli L D and Osbry E. Radioactive iodine therapy effect on functioning metastases of adenocarcinoma of the thyroid *J.A.M.A.* 132 838 847 (Dec) 1946
- 41 Seidlin S M Rosman I Osbry E., and Siegel E Radioiodine therapy of metastases from carcinoma of the thyroid a six year progress report *J Clin Endocrinol* 9 1122 1137 (Nov) 1949
- 42 Sherman R S and Ivker M Roentgen appearance of thyroid metastases in bone, *Am J Roentgenol* 63 196 203 (Feb) 1950
- 43 Stout A P Tumor seminar Texas State J Med 40 366 391 (Nov) 1944
- 44 Trevor W., and Pack G T The treatment of metastatic cancer of the thyroid *South Surgeon* 25 10 17 (Jan) 1949
- 45 Troell A Malignant goiter *Acta chir Scandinav* 94 533 549 (Nov) 1946
- 46 Trunnell J B., Marinelli L D Duffy B J., Jr Hill R Peacock W and Rawson R W The treatment of metastatic thyroid cancer with radioactive iodine credits and debits *J Clin Endocrinol* 9 1138 1152 (Nov) 1949
- 47 Ward R Symposium on surgical lesions of thyroid malignant goiter *Surgery* 16 783 803 (Nov) 1944
- 48 Warren S and Feldman J D The nature of lateral "aberrant" thyroid tumors *Surg Gynec. & Obst* 88 31-44 (Jan) 1949
- 49 Watson W L and Pool J L Cancer of thyroid *Surg Gynec & Obst* 70 1037 1050 (June) 1940
- 50 Wilensky A O and Kaufman P A Hurthle cell tumor of thyroid gland *Surg Gynec & Obst* 66 1 10 (Jan) 1938
- 51 Willis R A. Pathology of Tumors St Louis Mosby 1948 pp 601 615



FIG 219 CARCINOMA OF THYROID Age 60 Lump in throat for 12 years Loss of 20 lbs in 6 months Cough

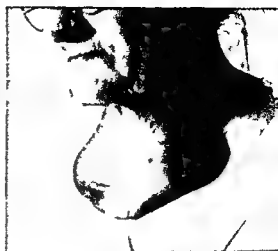


FIG 220 CANCER OF THYROID Inoperable Compare with Figure 236 showing similar growth due to lymphosarcoma



FIG 221 FETAL ADENOMA Irregular colloid deposits follicles and fetal cell masses separated Struma edematous and vascular Little scarring Low power ($\times 28$)



FIG 222 (Top left) ALVEOLAR ADENOMA with blood vessel and lymphatic invasion Verhoeff's elastic tissue stain accentuates elastica of blood vessels ($\times 72$) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 11:49, 1961)

FIG 223 (Top right) PAPILLARY ADENOCYSTOMA showing local invasion of capsule ($\times 72$) (Meissner W A and Lahey F H Carcinoma of thyroid in a thyroid clinic J Clin Endocrinol 8:749, 1961)



FIG 224 PAPILLARY ADENOCARCINOMA OF THYROID (See also Fig 225) Age 34 Götter noted 6 years increasing in size BMR minus 2⁰⁰ Pathologist suggested origin of tumor in an adenoma Operation followed by irradiation with recovery



FIG 225 PAPILLARY ADENOCARCINOMA OF THYROID REMOVED FROM PATIENT SHOWN IN FIGURE 224



FIG 227 CARCINOMA THYROID CROSS SECTION OF GROSS SPECIMEN Age 63 Six months duration Hard nodule to left of isthmus Question whether mass was carcinoma or localized thyroiditis Pathologic report papillary adenocarcinoma Treatment 10×200 r after surgery Patient returned 11 years later with an adenoma in right lobe which was removed Pathologic report adenoma In good health 3 years later (Lahey F H Hare H F and Warren S Carcinoma of the thyroid Ann Surg 112 977 1005)



FIG 226 PAPILLARY ADENOCARCINOMA MITOSIS ($\times 29$) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8 749 761)



FIG 228 ALVEOLAR ADENOCARCINOMA (x 28) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol ■ 749 :61)



FIG 229 SMALL CELL COMPACT CARCINOMA SIMPLEX (x 141) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol ■ 749 :61)



FIG 230 GIANT CELL CARCINOMA OF THYROID Age 64 Swelling in neck noted for 1 year Similar swelling stated to have been present at 18 and subsequently disappeared Roentgenogram revealed intrathoracic goiter which was partially calcified Symptoms hoarseness some dyspnea and pain in chest Weight loss 20 lbs Venous pressure 280 mm of water Larynx displaced to right and no action of left vocal cord seen Preoperative diagnosis adenomatous goiter possibly malignant At operation tumor was not adherent (confined to left lobe) removed in mass Pictures taken with infra red photography showing dilated veins Second photograph (right) 15 days after operation (See Fig 231 for microscopic) Roentgen therapy following operation No recurrence 4 years later

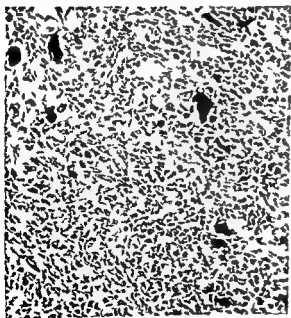


FIG 231 GIANT CELL CARCINOMA SIMPLEX ($\times 142$) (See also Fig 230) (Meissner W A and Labey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8 749 761)



FIG 232 LYMPH GLAND CONTAINING METASTATIC PAPILLARY ADENOCARCINOMA FREQUENTLY CALLED MALIGNANT ABERRANT THYROID (Warren S and Feldman J D The nature of lateral aberrant thyroid tumors Surg Gynec & Obst 88 31-44)



FIG 233 THYROGLOSSAL CYST AND DUCT Excised thyroglossal cyst and duct. A section of the hyoid bone is included as well as muscles up to the floor of the mouth. This was necessary in order to remove the tract completely and give a permanent cure.

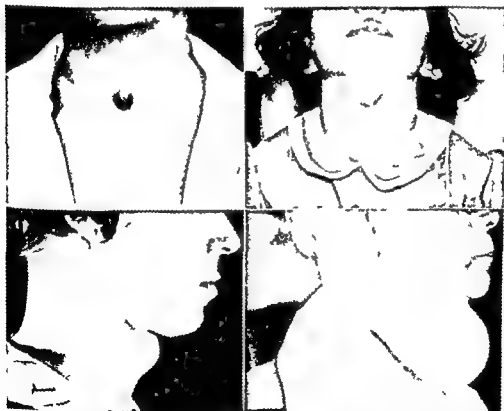


FIG 234 THYROGLOSSAL CYSTS Thyroglossal cysts in young, middle and elderly persons. Note midline position and tendency to enlarge. The cysts are usually located above the thyroid cartilage and very rarely below it. (Top left) Sinus (spontaneously formed) from thyroglossal cyst with faint outline of latter above it. (Top right) Small thyroglossal cyst with sinus opening just below it. (Bottom left) Medium sized thyroglossal cyst without a sinus. (Bottom right) Large thyroglossal cyst in elderly man (Clute H W and Smith L W. Carcinoma of the thyroid gland. Arch. Surg. 18:120).



FIG 230 GIANT CELL CARCINOMA OF THYROID Age 64 Swelling in neck noted for 1 year Similar swelling stated to have been present at 18 and subsequently disappeared Roentgenogram revealed intrathoracic goiter which was partially calcified Symptoms hoarseness some dyspnea and pain in chest Weight loss 20 lbs Venous pressure 280 mm of water Larynx displaced to right and no action of left vocal cord seen Preoperative diagnosis adenomatous goiter possibly malignant At operation tumor was not adherent (confined to left lobe) removed in mass Pictures taken with intra red photography showing dilated veins Second photograph (right) 15 days after operation (See Fig 231 for microscopic) Roentgen therapy following operation No recurrence 4 years later

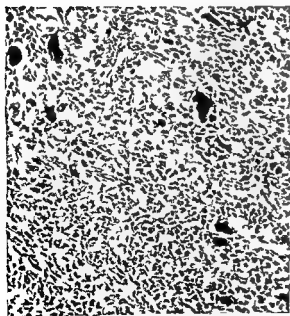


FIG 231 GIANT CELL CARCINOMA SIMPLEX ($\times 142$) (See also Fig 230) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8 749 761)



FIG 232 LYMPH GLAND CONTAINING METASTATIC PAPILLARY ADENOCARCINOMA FREQUENTLY CALLED MALIGNANT ABERRANT THYROID (Warren S and Feldman J D The nature of lateral aberrant thyroid tumors Surg Gynec & Obst 88 31 44)



FIG 233 THYROGLOSSAL CYST AND DUCT Excised thyroglossal cyst and duct. A section of the hyoid bone is included as well as muscles up to the floor of the mouth. This was necessary in order to remove the tract completely and give a permanent cure.

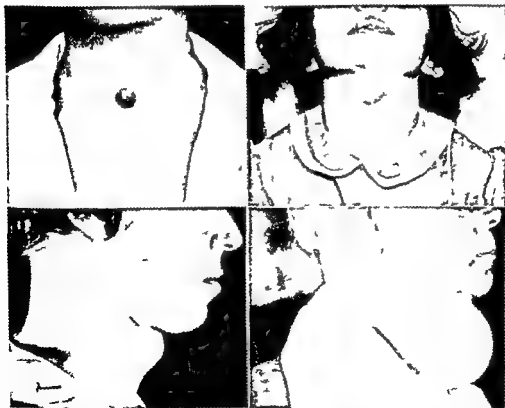


FIG 234 THYROGLOSSAL CYSTS Thyroglossal cysts in young, middle and elderly persons. Note midline position and tendency to enlarge. The cysts are usually located above the thyroid cartilage and very rarely below it. (*Top left*) Sinus (spontaneously formed) from thyroglossal cyst with faint outline of latter above it. (*Top right*) Small thyroglossal cyst with sinus opening just below it. (*Bottom left*) Medium sized thyroglossal cyst without a sinus. (*Bottom right*) Large thyroglossal cyst in elderly man. (Clute H. M. and Smith L. W. Carcinoma of the thyroid gland. Arch. Surg. 18:120)



FIG 235 LINGUAL THYROID TISSUE
Removed from base of tongue Myxedema
usually follows

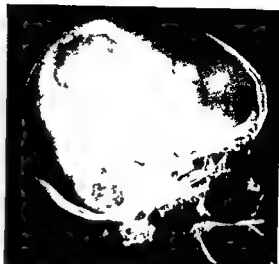


FIG 236 THYROID PAPILLARY ADENO-
CARCINOMA METASTATIC LESION IN SKULL
This type of lesion has been reported to
yield to radioactive iodine therapy after
total thyroidectomy



FIG 236 LYMPHOSARCOMA (Left) Tumor of neck suggesting malig-
nancy of thyroid. Biopsy showed lymphosarcoma Roentgen therapy
reduced size markedly (Right) Effect was only temporary

CHAPTER 4

Parathyroids

PRECLINICAL

Section 36 PRELIMINARY

- I HISTORY
- II ANATOMY
- III EMBRYOLOGY
- IV CONGENITAL ANOMALIES
- V HISTOLOGY
- VI FUNCTIONS
- VII CHEMISTRY
- VIII BIO ASSAY
- IX PATHOLOGY
- X CLASSIFICATIONS
- XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION
- XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION
- XIII EXAMINATION OF PATIENT

CLINICAL

Section 37 PRIMARY HYPOPARATHYROIDISM

38 PRIMARY HYPERPARATHYROIDISM

SECTION 36

PRELIMINARY

I HISTORY

- | | | |
|------|--------------------------------------|---|
| 1709 | Courtial ¹⁰ | Bone changes characteristic of osteitis fibrosa cystica noted |
| 1815 | Clarke ²¹ | Tetany described for first time |
| 1830 | Steinheim ⁴ | Parathyroid tetany differentiated |
| 1839 | Stanski ³ | Osseous lesions reported due to hyperfunctioning parathyroid glands |
| 1850 | Corvisart ¹ | The term 'tetany' was coined |
| 1855 | Remak ¹⁶ | First demonstration of the parathyroids |
| 1862 | Trousseau ⁴⁰ | A sign of tetany (Trousseau's sign) discovered |
| 1864 | Engel ¹⁸ | Case of generalized fibrocystic osteitis recorded (later pointed out by von Recklinghausen) |
| 1864 | Virchow ³⁸ | Parathyroid glands described |
| 1873 | Erb ¹⁹ | Increased irritability of motor nerve in tetany proved by electrical stimulation (Erb's sign) |
| 1876 | Chvostek ¹⁶ | A sign of tetany observed (Chvostek's sign) |
| 1880 | Sandstrom ¹⁹ | Lower set of glands found and named parathyroids |
| 1880 | Weiss ⁶² | Tetany recognized in humans following thyroidectomy |
| 1891 | Gley ³⁰ | Parathyroids are independent of thyroid gland |
| 1891 | von Recklinghausen ⁶⁰ | Osteitis fibrosa cystica reported |
| 1892 | Neumann ⁶¹ | Method for determining phosphorus |
| 1892 | von Eiselsberg ⁹ | Transplantation of parathyroids in thyroidectomized cats |
| 1893 | Chantemesse and Marie ⁸ | Variability in number of parathyroids in man |
| 1895 | Kohn ³⁶ | Anatomic and embryologic data on parathyroids |
| 1896 | Halsted ⁴ | Cases of chronic experimental tetany recorded |
| 1896 | Vasale and Generali ⁶⁷ | Removal of parathyroids probably cause tetany |
| 1898 | Lusena ²⁷ | Tetany treated by parathyroid emulsion and grafts |
| 1898 | Welsh ⁶³ | Histologic description of parathyroids |
| 1899 | Kocher ²⁴ | Parathyroid tumor noted |
| 1900 | de Santi ¹⁵ | He is usually accredited with first description of a parathyroid tumor |
| 1901 | Loeb ²⁴ | Inhibitory effect of calcium on muscular contraction proved |
| 1903 | Erdheim ⁴⁰ | Hyperplasia of parathyroids resulted from osteomalacia and rickets |
| 1904 | Albers-Schonberg ¹ | Condition of marble bones (osteopetrosis) discovered |
| 1904 | Askanazy ² | Cystic bone disease associated with parathyroid tumors reported |
| 1905 | MacCallum ⁶⁰ | Hypertrophy of the parathyroids occurred following certain diseases |
| 1907 | Forsyth ¹ | Marked variability of parathyroids in number size shape and position emphasized |
| 1907 | Parhon and Urechie ⁴³ | Intraperitoneal calcium ameliorated tetany in animals with thyroparathyroidectomy |
| 1909 | MacCallum and Voegtlin ⁶¹ | Hypocalcemia demonstrated as the etiology of tetany on removal of parathyroids |
| 1915 | Lyman ³⁸ | Method for determining calcium in urine and feces |

- 1915 Schlagenhauser³⁰ Parathyroid tumor caused von Recklinghausen's disease, i.e.,
osteitis fibrosa cystica
- 1917 Halverson and
Bergeim³¹, Lyman³²,
Marriott and
Howland⁴³ Procedure for analysis of blood calcium
- 1919 Huldshinsky³³ Curative effects of ultraviolet rays on rickets
- 1921 Steenbock, Sell
and Buell³⁴ Vitamin A separated from vitamin D
- 1922 Weil³⁵ Precocious puberty, pigmentation and peculiar variety of
osteopsathyrosis in a female
- 1923 Hanson³⁶ Effective parathyroid extract prepared
- 1923 Salvesen^{47 48} Toxic theory of tetany refuted and low blood calcium recog-
nized as the cause
- 1924 Berman⁷ Potent parathyroid extract made
- 1924 Steenbock and
Nelson³³, Hess³⁹ A ration which induced rickets in rats could be made anti-
rachitic by exposing it to ultraviolet light
- 1925 Collip¹² Parathyroid extract (parathormone) prepared and standardized
- 1925 Collip and Leitch¹⁴ First effective parathyroid extract in the treatment of tetany
due to hypoparathyroidism
- 1925 Mandl⁴ Successful removal of a parathyroid tumor from a patient
with bone cysts and calcinuria hyperparathyroidism thus
established
- 1926 Collip¹³ Experimental hyperparathyroidism produced hypercalcemia
and hypophosphatemia
- 1926 Jones³³ Cod liver oil used to prevent tetany in animals
- 1928 Gold³ Second case of von Recklinghausen's disease cured by sur-
gical removal of parathyroid tumor
- 1928 Urechia and
Popoviciu⁵⁰ Irradiated ergosterol given for postoperative tetany in man
- 1929 Albright and
Ellsworth² Primary action of parathyroids on phosphorus metabolism
postulated
- 1929 Barr, Bulger and
Dixon⁶ Term 'hyperparathyroidism' suggested
- 1930 Hannon, Shorr, Mc
Clellan and DuBois³ First demonstration of hypercalcemia in a patient with osteitis
fibrosa cystica (case of Captain Martell)
- 1931 Bourdillon et al.⁸ A crystalline compound 'calceiferol' isolated from irradiated
ergosterol which had 400 000 times the antirachitic value of
cod liver oil
- 1932 Askew et al.⁴, and
Windhaus et al.⁶¹ Pure crystals of vitamin D
- 1932 Hamilton and
Schwartz⁷ Method for determining small amounts of parathyroid hormone
- 1932 Hamilton and
Schwartz²⁰ Evidence presented for hyperfunction of parathyroid glands in
children with vitamin D deficiency
- 1933 Holtz³¹ Dihydrotachysterol (A T 10) introduced for treatment of
tetany
- 1937 Barney and
Sulkowitch⁵ Test for excess calcium in the urine

II ANATOMY¹³

A LOCATION AND DESCRIPTION

- 1 Shape
 - a Oval
 - b Disk
- 2 Color
 - a Yellow
 - b Reddish brown
- 3 Groups^{3 7}
 - a Upper pair
 - (1) Lateral lobes of thyroid
 - (a) On dorsum
 - (b) Within capsule
 - (c) In lobulations
 - (2) One on either side at level of lower border of cricoid cartilage, behind junction of pharynx and esophagus
 - b Lower pair
 - (1) Dorsum of lower border of lateral thyroid lobes
 - (2) Inferior to thyroid
 - (3) Within the mediastinum
- 4 Number^{3 8 11}
 - a From 2 to 12 may be present average 4
 - b More than 4—33 per cent
 - c Less than 4—1 per cent¹⁰

B SIZE

- 1 Length 3-15 mm
- 2 Width 2-6 mm
- 3 Thickness 0.5-4 mm

C WEIGHT

- 1 Range 20-40 mg
- 2 Average 35 mg
- 3 Total 1 Gm¹²
- 4 Greater in women⁹

D BLOOD AND LYMPH SUPPLY^{4 8 11}

- 1 Arteries (closely related to that of thyroid gland)
 - a Inferior thyroids
 - b Anastomatic channel between inferior or superior thyroid vessels
- 2 Veins—same as arterial supply
- 3 Lymph vessels—probably belong to the thyroid system

E NERVES

- 1 Laryngeals
 - a Recurrent
 - b Superior
- 2 Cervical sympathetic
- 3 No secretory nerves have been demonstrated¹

III EMBRYOLOGY¹⁻⁴

A ORIGIN—Entodermal cells which sprout from dorsolateral walls of third and fourth gill clefts

B FORMATION

1 Superior group

- a Primordium arises from fourth pouch adjacent to lateral thyroid body
- b Parts migrate cephalically to a position along the dorsal aspect near superior poles of thyroid lobes

2 Inferior group

- a Anlage is derived from third pouch just adjacent to the thymus
- b Portion becomes detached and migrates caudally to be embedded in the thyroid lobes

C TIME OF DEVELOPMENT—At 7 weeks (fetus—17 mm crown rump), parathyroids are associated with thyroid

IV CONGENITAL ANOMALIES

A VARIATIONS

- 1 Number and size
 - a Two to 12 glands^{3 4}
 - b Weight differs markedly
- 2 Blood supply

B ABERRANT TISSUE

- 1 In thyroid
- 2 Near larynx
- 3 At carotid sheath
- 4 Behind esophagus
- 5 In mediastinum
 - a Posterior
 - b Anterior
- 6 Within thymic rests
- 7 Near pericardium

C ABSENT¹V HISTOLOGY^{1-3 8 9}

A TYPES OF CELLS

- 1 Chief (principle water clear or wasser belle)
 - a Shape
 - (1) Large
 - (2) Round
 - b Cytoplasm
 - (1) Pale
 - (2) Clear
 - (3) Granules—rare
 - (4) Mitochondria
 - (5) Golgi apparatus

- Nucleus
 - (1) Large
 - (2) Spherical
- d Rich in glycogen
- Distinct membrane
- 2 Oxyphil (acidophil colloid)
 - a Shape
 - (1) Larger than chief cells
 - (2) Polygonal
 - b Cytoplasm
 - (1) Strongly acidophilic
 - (2) Granules
 - (a) Numerous
 - (b) Fine
 - (3) Mitochondria
 - (4) Golgi apparatus
 - c Nucleus
 - (1) Small
 - (2) Stain—deep
- 3 Intermediate
 - a Shape—variable
 - b Cytoplasm
 - (1) Paler than chief cells
 - (2) Stain—faint acid
 - (3) Granules
 - (a) Fine
 - (b) Less than in chief cells
 - c Nucleus
 - (1) Smaller than chief cells
 - (2) Stains darker than others
- B CELLULAR CORDS (see Fig 238)
 - 1 Arrangement
 - a Continuous masses of cells
 - b Columns
 - c Acini which occasionally contain colloid with small amounts of iodine
 - 2 Between groups of cells
 - a Fatty deposits which increase with age
 - b Sinusoidal capillaries
 - c Delicate fibrous or reticular stroma investing individual cells or cell groups
- C RELATIONSHIP OF CELLS
 - 1 Chief cells are more numerous than the oxyphils
 - 2 Sequence from masses to cords to acini is regarded by some as due to aging
 - 3 Functional relationship unknown
- D DISTRIBUTION OF CELLS AT VARIOUS AGES
 - 1 Fetus—cells arranged in loose reticular manner, except at periphery where there is a single layer of closely packed cells⁴
 - 2 Postnatal
 - a Chief or principal cells
 - (1) Round
 - (2) Cytoplasm scant
 - (3) Nucleus deeply stained
 - b Dark cells
 - (1) Round
 - (2) Cytoplasm
 - (a) Fine
 - (b) Granular
 - (c) Deep eosinophilic stain
 - 3 After age of seven
 - a Oxyphilic cells develop
 - (1) Large, polygonal shape
 - (2) Cytoplasm rich in eosinophilic granules
 - (3) Groups of 3 to 4, or single
 - (4) Later increase in number at periphery of gland
 - b Transition of different cellular types is seen
 - 4 Puberty
 - a Gland is of normal adult size
 - b Chief cells mostly
 - c Further increase in oxyphil cells
 - d Delicate capsule dips and divides gland into lobules
 - 5 Adult
 - a Glandular activity increased
 - b Fat deposits
 - c Colloid vesicles may be present
 - d Alveolar arrangement of cells may be found
 - e Cells may be columnar
 - f Further increase in oxyphil cells
 - g Blood vessels are numerous
- VI FUNCTIONS
 - A GLAND AS A WHOLE
 - 1 Chief purpose is to secrete parathyroid hormone however, it is not absolutely necessary to life
 - 2 It maintains and renders available the proper calcium and phosphorus ratio in the blood and the tissues, to which the skeleton can adapt its architecture to varying conditions (see 103 \ \ III for calcium phosphorus and bone metabolism)
 - 3 Relationship or dependence upon the pituitary gland has not been demonstrated conclusively

B HORMONE

1 Introduction

- Two sites of primary action of the parathyroid hormone have been postulated and both may be involved, depending on known and perhaps some unidentified factors^{1 2 10 17}

(1) Kidneys

- (a) Phosphate excretion is increased through decreased tubular resorption^{1 2 10 17 23 25}

- (b) Excretion of phosphate lowers the serum phosphorus

- (c) Serum calcium rises by an unknown mechanism in response to the decreased serum phosphorus

- (d) Hypercalcemia is associated with an increased urinary excretion of calcium however the latter may begin before the serum calcium level is above normal

- (e) Excess urinary excretion of calcium causes withdrawal of calcium from the bones if the daily intake is insufficient to balance the loss²²

- (f) If the primary action is also on the bones certain environmental conditions there may be necessary to provoke this effect (see below)

- (g) In support of the belief that a low serum phosphorus produces hypercalcemia a high intake of phosphorus in hyperparathyroidism raises the serum phosphorus and lowers the serum calcium to normal

- (h) Calcium is not drawn from the bones in hyperparathyroidism when the calcium intake is adequate for the bones will recalcify and a positive calcium balance can be established

(2) Bones

- (a) Several possibilities exist in liberation of calcium from the matrix

- (b) Osteoclastic formation and activity cause dissolution of bone^{2 11 16 17 18}

- [1] Stimulation is directly by parathyroid hormone

- [2] Response to stress or change in

- [a] Calcium phosphorus ratio

- [b] Other environmental factors

b The problem is not solved

- (1) Enzymes may be involved in this mechanism further studies are required¹⁹

- (2) The reader is referred to Al bright and Reifstein for further discussion on the pros and cons of the primary sites of action⁴

2 Functions as deduced from parathyroid hormone injections in normal or parathyroid deficient animals or men

a Urinary excretion¹¹

- (1) No alteration in creatine or creatinine until kidney damage occurs¹⁷

(2) Increased

- (a) Nitrogen (temporary)²⁴

- (b) Calcium¹²

- (c) Phosphate^{1 10 17}

- (d) Chlorides

- (e) Total volume

b Serum

(1) Decreased

- (a) Phosphorus (also lowered in corpuscular ester)^{1 6 8 17 20}

- (b) Chlorides

(2) Increased

- (a) Calcium²⁶

- (b) Magnesium (slight)⁴

- (c) Alkaline phosphatase if bone changes occur

(3) pH to acid side⁸c Fecal excretion—no consistent finding⁴

d Bones—see 36 VI D 2

e Gastro intestinal function is to maintain normal rate of calcium absorption⁷f Augmentation of vitamin D effect possibly through greater intestinal absorption¹⁹

C PARATHYROIDECTOMY (see 36 VI)^{5 11 15-18}

- 1 Neuromusculature
 - a Irritability
 - b Tetanic manifestations
 - c Psychic aberrations
 - d Cerebral calcification
 - e Intracranial pressure, if increased sufficiently may be followed by optic edema
 - f Hyperpyrexia³
- 2 Bones
 - a Skeletal density increased
 - b Osteoclastic activity decreased
 - e Abnormally soft (animals)
 - d Callous formation is delayed (animals)
 - e Osseous growth is not usually disturbed
- 3 Gastro intestinal
 - a Anorexia (animals, man)
 - b Aversion to phosphates
 - c Craving for calcium salts
 - d Diarrhea (animals, man)
 - e Interference with intestinal absorption of vitamins in the usual dietary quantities is probable¹³
 - f Calcium absorption is decreased and an ordinary intake of calcium is insufficient to control tetany
 - (1) Addition of from 5 to 10 times the usual intake of calcium will cause
 - (a) Calcium (serum) elevation
 - (b) Phosphorus (serum) reduction
 - (c) Increased excretion of urinary calcium
 - (2) Effectiveness of above is probably greater if some parathyroid function remains
- 4 Ectoderm^{6 7}
 - a Teeth
 - (1) Dentine defects^{8 11}
 - (2) Atrophy of odontoblasts (animals)
 - (3) Brittle⁸
 - b Loss of hair
 - c Nails
 - (1) Deformed
 - (2) Hypoplastic
- 5 Cataracts are common⁷
- 6 Urine
 - a Calcium—decreased (no calcium is

excreted below the serum level of 7 to 8 mg %, rare exceptions¹)

- b Phosphorus—decreased^{9 11}

7 Blood

- a Hemoconcentration
- b Sugar—normal
- e Protein (serum)—increased due to hemoconcentration
- d Calcium (serum)—decreased
- e Phosphorus (serum)—increased

8 Fecal calcium excretion increased

9 Pregnancy and offspring

- a Fertility decreased
- b Fetus is smaller than normal
- c Gestation is prolonged¹
[The above (a to c) are controlled in animals by a high calcium and/or low phosphorus intake]
- d Calcium cannot be mobilized from the bones (rats)

10 Herbivora (high calcium intake) are less sensitive than carnivora (high phosphorus intake)¹D HYPERHORMONAL EFFECTS (see 38)^{1 11}

- 1 Parathyroid glands—cytologic alterations of hyperfunction⁸
- 2 Bones
 - a Osteoclastic activity is increased eventually creating a loss of calcium with
 - (1) Resorption fibrosis
 - (2) Dense bone formation
 - (3) Picture of osteitis fibrosa cystica^{8-10 11, 14}
 - b Small and continued doses in animals may provoke only osteoblastic activity resulting in hard, sclerotic bone¹¹
 - c Calcification hypertrophy of epiphyseal cartilage develops in growing mice
- 3 Bodily changes
 - a Calcification of viscera^{8 11}
 - b Reduction in gastric
 - (1) Contents
 - (2) Acidity
 - c Hemorrhage into
 - (1) Gastro intestinal tract
 - (2) Bone marrow
 - d Growth is retarded (immature rats)
 - e Scleroderma-like condition¹³
 - f Dehydration

- 4 Urinary
 - a Output decreased
 - b Calcium increased¹
 - c Phosphorus increased¹
- 5 Blood
 - a Decrease in
 - (1) Chlorides (whole blood)
 - (2) Volume
 - b Increase in
 - (1) Red cells (hemoconcentration)
 - (2) Hemoglobin
 - (3) Nonprotein nitrogen (blood)
 - (4) Calcium (serum) (eventually falls)^{3 5}
 - (5) Phosphorus (serum)
 - (6) Viscosity
- 6 Fecal excretion—increased
 - a Calcium
 - b Phosphorus
- 7 Death
- 8 Other endocrine glands not affected significantly

E HISTOPHYSIOLOGY¹

- 1 Observations are fragmentary
- 2 Origin of secretion
 - a Chief cells are probably source of hormone
 - b Large water clear cells in abnormal conditions undoubtedly secrete hormone
 - c Oxyphil cells may be secretory
- 3 Oxyphilic cells increase with age and accumulate acidophilic protein, the significance of which is unknown
- 4 Inclusion bodies are found in some animals but not in man
- 5 Glycogen demonstrable in parenchyma (man)
- 6 Alkaline phosphatase is
 - a Present in endothelial walls of sinusoids (rats)
 - b Decreased slightly after hypophysectomy

F ACTIVITY AT DIFFERENT PERIODS IN LIFE

- 1 Parathyroids of the fetus may function during intra uterine life^{1 3}
- 2 Histologic variations from birth to senility suggest quantitative differences in elaboration of the hormone but actually very little is known

VII CHEMISTRY

A COMPOSITION OF HORMONE

- 1 Proteinlike substance which has never been isolated in pure form^{1 3 5}
- 2 Amorphous powder
- 3 Dried preparation contains
 - a Nitrogen 15.5 per cent
 - b Iron (traces)
 - c Sulfur (traces)

B PROPERTIES⁴

- 1 Destroy by boiling in
 - a Hydrochloric acid 10 per cent
 - b Sodium hydroxide, 5 per cent
 - c Pepsin at 37° C
 - d Tyrosine at 37° C
 - e Proteolytic enzymes
- 2 Soluble in
 - a Water
 - b Alcohol 80 per cent
- 3 Insoluble in
 - a Ether
 - b Acetone
 - c Pyridine

C PREPARATION¹

- 1 Extract is obtained by boiling fresh bovine parathyroid glands with aqueous hydrochloric acid
- 2 The hormone is precipitated with trinitrophenol
- 3 Precipitate is then extracted by acid acetone and alcohol and the hormone is reprecipitated with excess acetone
- 4 Final product is dissolved in water

VIII BIO ASSAY¹

A METHODS

- 1 Normal dogs (cats or rabbits)
 - a Unknown extract is injected subcutaneously into 10 animals (10-15 kg) and the rise in serum calcium is determined
 - b Test is not very satisfactory because of many variable factors
 - c One U.S.P. unit equals 1/100 of the amount of extract which increases the serum calcium 1 mg % within 16 to 18 hrs following a subcutaneous injection in normal dogs
 - d Parathyroid extract (U.S.P.) standardized of that 1 cc exerts specific activity of 80 to 120 units

- 2 Normal rats—determination of
 - a Increased urinary calcium
 - b Bone changes

IX PATHOLOGY

A Gross¹

- 1 Atrophy^{2 3}
- 2 Cysts
- 3 Adenomas (benign) or parathyroidoma (see 38 \ A 1 a)^{4 6 14 16 19}
 - a These outnumber simple hyperplasia in hyperparathyroidism
 - b Multiple tumor formation is difficult to distinguish from hyperplasia
- 4 Primary hyperplasia or hypertrophy (see 38 \ A 1 b)^{4 7 10}
- 5 Secondary hyperplasia causes enlargement, up to 30 times normal, of all the parathyroid glands¹
- 6 Carcinoma (see 38 \ A 1 c)^{1 14 17 18}

B Microscopic

- 1 Normal (see 36 IV)³
- 2 Atrophy (see 37 \ B 1 c)
- 3 Cysts (see 37 \ B 1 d)
- 4 Adenoma (see 38 \ B 1 a)
- 5 Primary hyperplasia (see 38 \ B 1 b)
- 6 Secondary hyperplasia (see 38 \ B 1 c)
- 7 Carcinoma (see 38 \ B 1 d)
- 8 Rare¹
 - a Inflammation
 - (1) Acute or chronic
 - (2) Miliary tuberculosis
 - (3) Syphilis
 - b Fibrosis—possibly as a result of inflammation but significance is questionable
 - c Passive congestion
 - d Infarction
 - e Hemorrhage
 - f Edema
 - g Colloid degeneration
 - h Fatty infiltration
 - i Amyloidosis
 - j Hydropic changes
 - k Metastatic involvement

C Histophysiology

- 1 Hypoparathyroidism
 - a In idiopathic type—no data on changes in remaining cells of parathyroids
 - b Bone—no histologic data
 - c Teeth—failure of dentine calcification^{9 10}

- d Eyes—deposition of calcium phosphate causing cataracts
- e Calcification in brain—no data
- f Calcium deposits however, do not occur in same tissues as in hyperparathyroidism¹¹

2 Hyperparathyroidism

- a Parathyroid gland
 - (1) No proven relationship between
 - (a) Types of cells
 - (b) Clinical picture
 - (2) Changes which suggest an excess secretion are absent, except for an increased number of cells
 - (3) Follicles and colloid are seen more frequently in hyperparathyroid adenomas

b Bones¹²

- (1) Osteoclasts and osteoblasts increase over the normal number with bone involvement
- (2) When excessive parathyroid activity ceases, osteoclasts disappear while the osteoblasts remain as well as cover areas occupied by the former
- (3) Deposition of calcium in osteoid areas takes place slowly
- (4) Cysts with fibrous tissue may also recalcify after osteoid tissue has been laid down

c Calcium deposits are found in many tissues, if blood level is very high¹¹

- (1) Conjunctivae
- (2) Corneae
- (3) Lungs
- (4) Stomach
- (5) Kidney tubules
- (6) Muscles

3 Other conditions which alter cells

- a Hypoplasia
 - (1) Parathyroid tumor of one or more glands causes hypoplasia of the others
 - (2) Moniliasis
 - (3) Constant use of parathyroid hormone
- b Hyperplasia of chief cells principally may be preceded by
 - (1) Avitaminosis D
 - (2) Renal failure
 - (3) Malignant metastases to bone
 - (4) Acromegaly

- 4 Urinary
 - a Output decreased
 - b Calcium increased¹
 - c Phosphorus increased¹
- 5 Blood
 - a Decrease in
 - (1) Chlorides (whole blood)
 - (2) Volume
 - b Increase in
 - (1) Red cells (hemoconcentration)
 - (2) Hemoglobin
 - (3) Nonprotein nitrogen (blood)
 - (4) Calcium (serum) (eventually falls)^{3, 5}
 - (5) Phosphorus (serum)
 - (6) Viscosity
- 6 Fecal excretion—increased
 - a Calcium
 - b Phosphorus
- 7 Death
- 8 Other endocrine glands not affected significantly

E HISTOPHYSIOLOGY¹

- 1 Observations are fragmentary
- 2 Origin of secretion
 - a Chief cells are probably source of hormone
 - b Large water clear cells in abnormal conditions undoubtedly secrete hormone
 - Oxyphil cells may be secretory
- 3 Oxyphilic cells increase with age and accumulate acidophilic protein the significance of which is unknown
- 4 Inclusion bodies are found in some animals but not in man
- 5 Glycogen demonstrable in parenchyma (man)
- 6 Alkaline phosphatase is
 - a Present in endothelial walls of sinusoids (rats)
 - b Decreased slightly after hypophysectomy

F ACTIVITY AT DIFFERENT PERIODS IN LIFE²

- 1 Parathyroids of the fetus may function during intra uterine life^{1, 3}
- 2 Histologic variations from birth to senility suggest quantitative differences in elaboration of the hormone but actually very little is known

VII CHEMISTRY

A COMPOSITION OF HORMONE

- 1 Proteinlike substance which has never been isolated in pure form^{1, 3, 5}
- 2 Amorphous powder
- 3 Dried preparation contains
 - a Nitrogen 15.5 per cent
 - b Iron (traces)
 - c Sulfur (traces)

B PROPERTIES^{1, 4}

- 1 Destroy by boiling in
 - a Hydrochloric acid, 10 per cent
 - b Sodium hydroxide, 5 per cent
 - c Pepsin at 37° C
 - d Tyrosine at 37° C
 - e Proteolytic enzymes
- 2 Soluble in
 - a Water
 - b Alcohol 80 per cent
- 3 Insoluble in
 - a Ether
 - b Acetone
 - c Pyridine

C PREPARATION¹

- 1 Extract is obtained by boiling fresh bovine parathyroid glands with aqueous hydrochloric acid
- 2 The hormone is precipitated with trinitrophenol
- 3 Precipitate is then extracted by acid acetone and alcohol and the hormone is reprecipitated with excess acetone
- 4 Final product is dissolved in water

VIII BIO ASSAY¹

A METHODS

- 1 Normal dogs (cats or rabbits)
 - a Unknown extract is injected subcutaneously into 10 animals (10-15 kg) and the rise in serum calcium is determined
 - b Test is not very satisfactory because of many variable factors
 - c One USP unit equals 1/100 of the amount of extract which increases the serum calcium 1 mg % within 16 to 18 hrs following a subcutaneous injection in normal dogs
 - d Parathyroid extract (USP) standardized of that 1 cc exerts specific activity of 80 to 120 units

- b Arteriosclerosis
- 2 Genito urinary system
 - a Polyuria
 - b Renal
 - (1) Colic
 - (2) Stones
 - (3) Sand
 - (4) Failure (uremia)
- 3 Musculature
 - a Myalgia
 - b Atony
- 4 Serum
 - a Calcium range—11 to 18 mg %
 - b Phosphorus—below 4 mg %
- 5 Bones
 - a Pathologic fractures
 - b Shrinkage of height
 - (1) Scoliosis
 - (2) Kyphosis
 - (3) Bowing of legs
 - c Epulides
 - d Cysts
 - e Localized pain
- (b) Positive sign is a quick contraction of
 - [1] Entire lower portion of face
 - [2] Side of upper lip only
- (2) Trousseau
 - (a) Tourniquet or sphygmomanometer cuff is placed around upper arm
 - (b) Pulse need not be obliterated, but pressure equivalent to diastolic pressure should be maintained for 5 min
 - (c) Typical main en griffe or main d'accoucheur indicates a positive test
 - (d) Same test may be applied to lower extremities
- (3) Erb
 - (a) Median nerve in adults or peroneal nerve in children is stimulated by an electrical current
 - (b) The neuromuscular response to galvanic stimulation is obtained with weaker currents in tetany than in normal individuals
 - [1] Judgment and experience in performance of the test are necessary hence it is of limited value
 - [2] Children under 5 years are less responsive
 - (c) Positive reaction to stimulation
 - [1] Muscles contract by cathodal opening current of less than 5 milli amperes
 - [2] Anodal opening current is less than anodal closing current (less current is required to obtain a response on opening the circuit when the positive electrode is applied than if the circuit is closed)
- (4) Schlesinger
 - (a) The leg is held at the knee

XIII EXAMINATION OF PATIENT

A HYPOPARATHYROIDISM

- 1 History
 - a Patient may have no symptoms
 - b Tingling or numbness of
 - (1) Face
 - (2) Lips
 - (3) Extremities
 - c Mental depression marked anxiety
 - d Failing vision
 - e Convulsive or tetanic seizures
 - f Retarded development if disease occurs during growth period
- 2 Physical status
 - a Hair—for alopecia
 - b Eyes
 - (1) Cataracts
 - (2) Photophobia
 - (3) Keratoconjunctivitis
 - c Teeth—structural defects (see 37 VI F)
 - d Neuromuscular tests
 - (1) Chvostek
 - (a) Skin over middle branch of facial nerve (anterior to external auditory meatus) is tapped lightly with
 - [1] Finger
 - [2] Percussion hammer
 - [3] Pencil or pen

K CLASSIFICATIONS

A COMPREHENSIVE LIST OF POSSIBLE FACTORS—see 2 VIII A

B HORMONAL

- 1 Pseudohypoparathyroidism or euparathyroidism with an absence of target organ response
- 2 Hypoparathyroidism or deficiency of parathyroid hormone
- 3 Hyperparathyroidism or excess of parathyroid hormone
 - a Primary
 - b Secondary

C CLINICAL

- 1 Parathyroid tumors with euparathyroidism
- 2 Pseudohypoparathyroidism
- 3 Hypoparathyroidism
 - a No tetany
 - b Latent tetany
 - c Manifest tetany
- 4 Hyperparathyroidism
 - a Primary
 - (1) Chronic
 - (a) Chemical changes only
 - [1] Hypercalciuria
 - [2] Hypercalcemia
 - [3] Hypophosphatemia
 - (b) Renal involvement
 - (c) Bone disease
 - [1] Osteitis fibrosa cystica
 - [2] Osteitis fibrosa generalisata
 - (d) Bone and renal disease
 - (2) Acute—with any of the above conditions
 - b Secondary
 - (1) Avitaminosis D or resistance to it
 - (a) Rickets (children)
 - (b) Osteomalacia (adults)
 - (2) Steatorrhea
 - (3) Other causes of calcium deprivation
 - (a) Inadequate calcium intake
 - (b) Pregnancy [with b (1)]
 - (c) Lactation [with b (1)]
 - (4) Renal disease
 - (a) Tubular insufficiency and renal acidosis—Milkman's syndrome
 - (b) Glomerular insufficiency

with renal osteitis fibrosa cystica

[1] Nephritis

[2] Congenital malformation of genito urinary tract

(c) Hyperamino aciduria—Fanconi's syndrome

XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION

A SUMMARY (see 37)

- 1 Mental changes
 - a Retardation
 - b Delirium
 - c Anxiety
 - d Depression with sense of impending disaster
- 2 Cerebral calcification
- 3 Neuromuscular
 - a Hyperexcitability effects may be
 - (1) Mild
 - (2) Severe as in tetany
 - b Numbness and tingling of extremities
 - c Stiffness of facial muscles especially about lips
 - d Spasm
 - (1) Eyelids
 - (2) Laryngeal
 - (3) Carpopedal
 - (4) Anal
 - e Abdominal rigidity
 - f Strabismus
 - g Convulsions
- 4 Ectodermal defects of
 - a Hair
 - b Teeth
 - c Nails
- 5 Cataracts
- 6 Serum
 - a Calcium—below 9 mg %
 - b Phosphorus—above 4 mg %
- 7 Bone density increased

XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION

A SUMMARY (see 38)

- 1 General
 - a Vague complaints of ill health
 - (1) Anorexia
 - (2) Weight loss
 - (3) Weakness
 - (4) Polydipsia

- d Alkaline phosphatase
- (1) Normal, if no bone pathology
 - (2) Values over 5 Bodansky units indicate bone changes which are proportional to degree of activity
- 4 Methods for special procedures
- Sulkowitch test⁴
- (1) Purpose
 - (a) In patients with tetany, the presence of more than a trace of urinary calcium is against hypocalcemia, with rare exceptions
 - [1] Possibly low renal threshold for calcium excretion
 - [2] Renal infection⁴
 - (b) Regulation of medication in hypoparathyroidism by checking urine and adjusting dosage according to the results (The patient can do this)
 - (c) To rule out hyperparathyroidism in patients with
 - [1] Kidney stones or rare healed bones
 - [2] Equivocal serum calcium and phosphorus values
 - (2) Method
 - (a) Five cc of urine specimen
 - (b) Two cc of Sulkowitch solution
 - (c) The speed (3 to 30 sec) of appearance and amount of precipitate (zero to 4 plus) are to be noted
 - (d) Test may be modified by a special low calcium diet for 5 to 7 days which includes no milk milk products or eggs but only the following
 - [1] Orange juice
 - [2] Rice
 - [3] Cream of wheat
 - [4] Bread
 - [5] Uneda biscuits
 - [6] Margarine
 - [7] Bacon
 - [8] Lean meat
 - [9] Potato
 - [10] Applesauce
 - [11] Bananas
 - [12] Tomatoes
 - [13] Salt and pepper
 - [14] Sugar
 - [15] Tea
 - [16] Coffee
 - (e) Twenty four hr urine collected on last day of diet
 - (f) Two hundred mg or more of calcium/24 hrs is probably abnormal but is not pathognomonic
- (3) Results
- (a) Negative test (no precipitate)
 - [1] Indicates hypocalcemia (less than 7.5 mg %)
 - [2] Rules out hyperparathyroidism
 - (b) Three to 4 plus (heavy white cloud) suggests hypercalcemia (greater than 10.5 mg %)
- b Ellsworth Howard test⁴
- (1) Purpose—to aid in diagnosis of hypoparathyroidism
 - (2) Method
 - (a) Two cc (200 units) of parathyroid extract is given intravenously to a fasting individual
 - (b) Phosphorus content of urine specimens is determined at hourly intervals for 3 hrs before the injection and 3 to 5 hrs after it
 - (3) Results of phosphate excretion
 - (a) Normal—increased
 - (b) True hypoparathyroidism—sharp rise and a quick fall
 - (c) Pseudohypoparathyroidism—slight or no change
 - (d) Hyperparathyroidism
 - [1] Probably no increase if glands secreting at maximum capacity (see 38 XIII B 1 a (4))
 - [2] No data available
- c Renal function tests—of value in connection with differential diagnosis of parathyroid disorders
- (1) Concentration test
 - (a) Purpose—to determine function of tubules
 - (b) Method

and is forcibly flexed at the hip joint

(b) Positive test—If extensor spasm occurs at the knee joint with plantar flexion of the foot

(5) Pool—positive result if carpal spasm develops with forced abduction of the arm

(6) Lust—tapping peroneal nerve results in muscular contraction

(7) Escherich—tapping at the angle of the mouth causes forward propulsion of the lips

(8) Schultz—tapping the tongue produces a concave upper surface

(9) Weiss—tapping the temporal branch of facial nerve results in contraction of the following muscles

(a) Frontal

(b) Orbicular

(c) Superciliary

(10) Hoffman—mechanical irritation of trigeminal nerve may elicit local pain

3 Laboratory data—findings are usually negative, except the following

a Sulkowitch test (see 36 XIII B 4 a)

(1) Negative

(2) No calcinuria if serum calcium is below 7 to 8 mg % occasional exceptions

b Serum protein, albumin and globulin should be checked if any reason exists to question the calcium and phosphorus levels (see 103 X G)

c Serum calcium

(1) Below 9 mg % usually rarely lower than 5 mg %

(2) Between 9 to 10 mg % some times in true hypoparathyroidism in which case the serum phosphorus is high

d Serum phosphorus

(1) Above 4 mg % in majority of cases

(2) If equivocal findings take fast mg sample or one at least 6 hrs after eating

e Basal metabolic rate and plasma cholesterol are done in patients with history of previous hyperthyroidism

4 Roentgenographic findings¹

a Teeth—blunted roots in cases beginning in childhood

b Bones—osteomalacia is possible if parathyroid deficiency starts in childhood

II HYPERPARATHYROIDISM

1 History

a No symptoms

b Renal

(1) Colic

(2) Stones

(3) Sand

(4) Polyuria

c Polydipsia

d Bone pain

e Spontaneous fracture

f Muscular hypotonia

II Unexplained

(1) Fatigue

(2) Anorexia

(3) Vomiting

2 Physical status

a Extremities

(1) Various abnormalities

(2) Fractures

b Spine

(1) Round back

(2) Scoliosis

(3) Kyphosis

c Eyes—special examination by ophthalmologist may reveal specific changes (see 37 VI F)

d Teeth—occasionally malposed

e Neck—tumor may be palpable in lateral aspects of thyroid in rare instances

f Chest may be deformed

3 Laboratory data

a Sulkowitch test (see below)

b Serum calcium

(1) Over 11 to 18 mg % usually

(2) If normal and other evidence is strong Ellsworth Howard test may be performed and should be negative (see 36 XIII B 4 b)

c Serum phosphorus

(1) Fasting level should be determined

(2) Level below 4 mg % usually

(3) Concentration should be less than 3 mg % to be significant unless renal damage is found

- urine/min or 75 to 130 per cent
- [2] Nephritis—between 10 and 30 cc or below 50 per cent
- (5) Inulin clearance
- (a) Purpose—to check glomerular filtration
- (b) Method
- [1] Procedure can be started any time of day
- [2] Height and weight are taken to calculate surface area
- [3] Patient should be reclining
- [4] Patient takes a glass of water at 8 30 A M and every $\frac{1}{2}$ hr until test is finished
- [5] One half glass of milk and 1 slice of toast and butter at 9 30 A M
- [6] At 10 00 A M ($1\frac{1}{2}$ hrs after starting test) blood sample is taken
- [7] Ten Gm of inulin dissolved in 100 cc of sterile saline solution at body temperature is injected intravenously at the rate of 10 cc/min
- [8] Bladder is emptied 1 hr after completion of injection and specimen is discarded
- [9] Urine specimens 2 and 3 hrs after injection are measured accurately and timed
- [10] Blood samples are taken $1\frac{1}{2}$ and $2\frac{1}{2}$ hrs after injection of inulin
- [11] Analysis for inulin is made by colorimetric method
- (c) Results
- [1] Normal—for a surface area of 1.73 sq meters, the average clearance is about 120 cc/min (volume of glomerular filtrate)
- [2] Abnormal
- [a] Nephrosis — decreased slightly
- [b] Acute or subacute nephritis — decreased moderately
- [c] Chronic hemorrhagic nephritis—decreased markedly (20 cc or less)
- (6) Diodrast clearance
- (a) Purpose — total mass of functional renal tissue and rate of blood flow can be determined (tubular excretory mass is measured)
- (b) Method
- [1] Part one
- [a] Patient should be reclining during test
- [b] Height and weight are taken for calculation of body surface area
- [c] Breakfast of toast butter and $\frac{1}{2}$ glass of milk is taken at any convenient time
- [d] 1000 cc of water is taken 2 hrs before starting the test
- [e] 200 cc of water is given every half hour until the end of the test unless administration of fluid is contraindicated
- [f] Two hrs after a liter of water has been taken, blood and urine samples are collected
- [g] Five cc of 35 per cent diodrast is injected intravenously noting the exact time
- [h] Fifteen min after the injection bladder is emptied, urine is discarded and exact time is recorded

- [1] After supper and until procedure is over patient does not take any thing by mouth
- [2] Bladder emptied on retiring and urine is discarded
- [3] All urine voided during the night is saved including first passed in the morning and labeled No 1
- [4] One hr later, patient voids specimen No 2 collected
- [5] One hr after that voids again and No 3 specimen obtained
- [6] All three specimens tested for specific gravity

(c) Results

- [1] Normal — at least one urine sample should have a specific gravity between 1.025 and 1.032
- [2] Severe impairment — specific gravity below 1.010 in all

(2) Dilution test

- (a) Purpose—to evaluate function of tubules

(b) Method

- [1] No breakfast
- [2] Bladder emptied
- [3] 1,500 cc of water taken (9:00 A.M.)
- [4] At 30 min intervals 8 urine specimens are collected
- [5] From 12:00 noon to 8:00 A.M. next morning all the urine is saved in one container
- [6] Volume of each sample is measured
- [7] Specific gravity determined

(3) Phenolsulfonphthalein (PSP) test

- (a) Purpose—to test the ability of the kidneys to excrete the dye

(b) Method

- [1] Patient takes 2 glasses (300 to 400 cc) of water
- [2] Twenty min later, bladder emptied
- [3] One cc of phenolsulfonphthalein dye injected either
 - [a] Intramuscularly
 - [b] Intravenously
- [4] Urine specimens are saved after injection
 - [a] Intramuscular — 1 hr 10 min and 2 hrs 10 min
 - [b] Intravenous — 15 and 30 min

(c) Results of dye excretion

- | | |
|---------------------|-------------------|
| [1] Normal | PER CENT |
| [a] 1st sample | 40-50 |
| [b] 2nd sample | 20-25 |
| [c] Total excretion | 60-75 |
| [2] Impairment | PER CENT OF TOTAL |
| [a] Slight | 40-59 |
| [b] Moderate | 25-39 |
| [c] Marked | 11-24 |
| [d] Maximal | 0-10 |

(4) Urea clearance

- (a) Purpose—to study total function of kidneys

(b) Method

- [1] Patient should be fasting
- [2] Patient voids discards specimen and records exact time
- [3] Two glasses of water are taken
- [4] Blood specimen drawn $\frac{1}{2}$ hr after test starts
- [5] At end of an hour, patient voids again recording exact time
- [6] Total urine specimen
- [7] Number of cc of blood cleared of urea by 1 cc of urine/min is determined

(c) Results

- [1] Normal — any figure above 40 cc of blood cleared by 1 cc of

- 3 Askanazy M Über Ostitis deformans ohne osteoides Gewebe Arb a d path Anat Inst Tubingen 4 398 422 1904
- 4 Askew F A Bourdillon R H Bruce H M Callow R K Philpot J St L and Webster T A Crystalline vitamin D Proc Roy Soc London 109 488 506 1932
- 5 Barney J D and Sulkowitch H W Progress in the management of urinary calculi J Urol 37 746 762 (June) 1937
- 6 Barr M P, Bulger H A and Dixon H H Hyperparathyroidism JAMA 92 951 952 (Mar) 1929
- 7 Berman L A crystalline substance from the parathyroid glands that influences the calcium content of the blood Proc Soc Exper Biol & Med 21 465 1924
- 8 Bourdillon R H Bruce H M Fischmann C and Webster T A The quantitative estimation of vitamin D by radiography Med Research Council London His Majesty's Stat Off Report No 158 1931
- 9 Chantemesse A and Marie R Les glandes parathyroïdiennes de l'homme Bull et mem Soc med d'hop de Paris 10 202 204 (Mar) 1893
- 10 Chvostek F Sr Beitrag zur Tetanie Wien med Pr 17 1201 1203 1225 1253 (Sept) and 1313 (Oct) 1876
- 11 Clarke J Commentaries on Some of the Most Important Diseases of Children London 1815 pp 78 98
- 12 Collip J B The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium J Biol Chem 63 395 438 1925
- 13 — The parathyroid glands Medicine 5 1 57 (Feb) 1926
- 14 Collip J B and Leitch D B A case of tetany treated with parathyrin Canad M A J 15 59 60 1925
- 15 Corvisart L De la contracture des extremités ou tetanies Paris 1850
- 16 Courtial J J Sur la fragilité des os I Nouvelles observations anatomiques Marchand Libraire 1709 pp 33 37
- 17 de Santi Parathyroidgeschwulst Symptome von maligner Erkrankung des Larynx hervorruhend Internat Centralbl f Larynx u Rhinol 16 546 547 1900
- 18 Engel G Ueber einem Fall von cystoïder Entartung des ganzen Skelettes Giessen Pietsch 1864
- 19 Erb W H Zur Lehre von der Tetanie nebst Bemerkungen über die Prüfung der electrischen Erregbarkeit motorischer Nerven Arch Psychiat Nervenkr 4 271 316 1873
- 20 Erdheim J Zur normalen und pathologischen Histologie der Glandula thyroidea parathyroidea und Hypophysis Beitr z path Anat = z allg Path 33 58 236 1903
- 21 Forsyth D Observations on the parathyroids and accessory thyroids in man Brit M J 1 372 373 1907
- 22 Gley E Sur les fonctions du corps thyroïde Compt rend Soc de biol 3 841 847 1891
- 23 Gold E Ueber die Bedeutung, der Epithelkorpervergrosserung bei der Ostitis fibrosa generalisata Recklinghausen Mitt a d Grenz geb d Med u Chir 41 63 87 1928
- 24 Halsted W S An experimental study of the thyroid gland of dogs with especial consideration of hypertrophy of this gland Johns Hopkins Hosp Rep 1 3/8 1896
- 25 Halverson J O and Bergum O The determination of small amounts of calcium particularly in blood J Biol Chem 32 159 170 (Nov) 1917
- 26 Hamilton H L K and Schwartz C Rickets and hyperparathyroidism J Clin Investigation 11 817 (July) 1932
- 27 — A method for the determination of small amounts of parathyroid hormone J Pharmacol & Exper Therap 46 285 292 (Nov) 1932
- 28 Hannon R R Shorr E McClellan W S and DuBois E F Case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of parathyroid bodies metabolic study J Clin Investigation 8 215 227 (Feb) 1930
- 29 Hanson A M An elementary chemical study of the parathyroid glands of cattle Mil Surgeon 52 280 284 (Mar) 1923
- 30 Hess A F Experiments on the action of light in relation to rickets Am J Dis Child 28 517 518 (Oct) 1928
- 31 Holtz F Die Behandlung der postoperativen Tetanie Arch f Klin Chir 177 32 34 1933
- 32 Huldshinsky K Care of rachitis by means of artificial heliotherapy Deutsche med Wchnchr 45 712 (June) 1919
- 33 Jones J H The effect of administration of cod liver oil upon thyroparathyroidectomized dogs J Biol Chem 70 647 657 (Nov) 1926
- 34 Kocher T Ueber glykogenhaltige Strumen Virchows Arch 155 532 556 (Mar) 1899
- 35 Kohn A Studien über die Schilddrüse Arch f mikr Anat 44 366 422 1893
- 36 Loeb J On an apparently new form of muscular irritability produced by solution of salts whose anions are liable to form insoluble calcium compounds Am J Physiol 5 352 373 1901
- 37 Lusena G Cisti ad epiteliu cirliato in glandole paratiroidee externe Anatam Anzeiger 15 52 56 1898
- 38 Lyman H A rapid method for determining calcium in urine and feces J Biol Chem 21 551 556 (July) 1915
- 39 — A rapid method for determining calcium in blood and milk J Biol Chem 29 169 178 (Mar) 1917
- 40 MacCallum W G The pathology of tetany Johns Hopkins Hosp Bull 16 143 149 (Apr) 1903
- 41 MacCallum W G and Voegtlin C On the relation of tetany to the parathyroid glands and to calcium metabolism J Exper Med 11 118 151 1909
- 42 Mandl F Therapeutischer Versuch bei Ostitis fibrosa Generalisata Mittels Extirpation eines Epithelkörperchentumors Wien klin Wchnschr 33 1343 1344 1925
- 43 Marmott W M and Howland J A micro method for the determination of calcium and magnesium in blood serum J Biol Chem 32 233 239 (Nov) 1917
- 44 Neumann A Einfache Veraschungsmethode (Säuregemisch Veraschung) und Vereinfachte Bestimmungen von Eisen Phosphorsäure Salzsäure und anderen Aschenbestandtheilen unter Benutzung dieser Säuregemisch Veraschung Ztchr f Phys Chemie 37 115 142 1902
- 45 Parhon C and Uréche C S Untersuchungen

- [i] Blood is drawn 10 and 20 min after initial emptying of bladder, noting the time
- [j] Collect all urine excreted 30 min after initial emptying of bladder
- [k] Blood and urine specimens are analyzed for iodine
- || Part two
 - [a] Patient drinks 500 cc of water after above procedure
 - [b] Thirty min later 30 cc of 35 per cent diodrast is injected intravenously
 - [c] Bladder emptied and urine is discarded
 - [d] Blood sample is collected 5 and 10 min after voiding observe exact time
 - [e] Collect urine specimen 20 min after emptying bladder record time accurately
 - [f] Blood and urine specimens are analyzed for iodine
- || Results
 - [a] Diodrast plasma clearance averages 566 cc of blood/min range from 424 to 754 cc/min
 - [b] Renal blood flow averages 940 cc of blood/min range from 710 to 1260 cc/min
 - [c] Tubular excretory mass averages 36 mg of diodrast iodine/min range is 25 to 47 mg/min
- d Hamilton Schwartz (H S) test⁴⁹
 - (1) Indication—study of conditions in which hyperparathyroid activity might be present or suspected
 - (2) Method
 - (a) Standardized and especially prepared rabbit is required
 - (b) Calcium chloride (100 mg in 10 cc of water) is administered by stomach tube to the rabbit at beginning of test, 1, 3 and 5 hrs
 - (c) Patient's blood (30 cc) is injected into rabbit's thighs (15 cc into each)
 - (d) Calcium in the rabbit's blood is determined before the test and 7 to 15 min after last 2 doses of calcium
 - (3) Result—positive test if blood calcium increases at least 0.3 millimols/liter after the third or fourth administration of calcium chloride
- 5 Roentgenologic examination
 - a Teeth are checked for absence of lamina dura in cases of hyperparathyroidism with bone involvement
 - b Skull to find
 - (1) Changes in tables
 - (2) Bone cysts especially in maxilla
 - c Pelvis and long bones should be studied for abnormalities (see 38 VII)
 - d Kidneys for
 - (1) Stones
 - (2) Calcification
- 6 Chemical analysis of renal stones
- 7 Bone biopsy to identify type of lesion

REFERENCES

I HISTORY

- 1 Albers Schonberg H F Röntgenbilder einer seltenen Knochenerkrankung Fortschr d Geb d Röntgenstr 7 188 190 1903 1904

- 2 Albright F and Ellsworth R Studies on the physiology of the parathyroid glands calcium and phosphorus studies on case of idiopathic hypoparathyroidism J Clin Investigation 7 183 201 (June) 1929

V HISTOLOGY

- 1 Fischer, E Die Glandulae parathyreontae des Menschen Arch f Anat u Entwicklungsgesch Leipzig pp 133 162 1911
- 2 Kohn A Studien über die Schilddrüse Arch f mikr Anat 44 366 422 1895
- 3 Maximow A A and Bloom W A Textbook of Histology ed 2 pp 307 308 Philadelphia Saunders 1935
- 4 Norris E H Anatomical evidence of prenatal function of the human parathyroid glands Anat Rec 96 129 142 (Oct) 1946
- 5 Smith P E Copenhaver W M Severinghaus A E and Goss C M in Bailey's Textbook of Histology ed 11 p 665 Baltimore Williams & Wilkins 1944
- 6 Welsh D A Concerning the parathyroid glands a critical anatomical and experimental study J Anat & Physiol 32 380 402 (Apr) 1898

VI FUNCTIONS

Hormone

- 1 Albright F Bauer W Ropes M and Aub J C Studies of calcium and phosphorus metabolism I The effects of the parathyroid hormone J Clin Investigation 7 139 181 (Apr) 1929
- 2 Albright F Burnett C H Parson W Reifstein E C and Roos A Osteomalacia and late rickets Medicine 25 399-479 (Dec) 1946
- 3 Albright F and Ellsworth R Studies on the physiology of the parathyroid glands calcium and phosphorus studies on a case of idiopathic hypoparathyroidism J Clin Investigation 7 183 201 (June) 1929
- 4 Albright F and Reifenstein E C Jr The Parathyroid Gland and Metabolic Bone Diseases p 15 Baltimore Williams & Wilkins 1948
- 5 Albright F Sulkowitch H W and Bloomberg E A comparison of the effects of vitamin D dihydrotachysterol (A T 10) and parathyroid extract on the disordered metabolism of rickets J Clin Investigation 18 165 169 (Jan) 1939
- 6 Aub J C Calcium and phosphorus metabolism Harvey Lect (1928 1929) 24 151 174 1929
- 7 Bauer W Albright F and Aub J C Case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of parathyroid bodies metabolic study J Clin Investigation 8 229 248 (Feb) 1930
- 8 Brehme T and Gyorgy P Stoffwechselwirkung und klinische Verwendbarkeit des Epithelkörperchenhormons (Collip) Jahrb f Kinderheilk 118 143 177 (Dec) 1927
- 9 Collip J H Pugsley L I Selye H and Thomson D L Observations concerning mechanism of parathyroid hormone action Brit J Exper Path 15 335 336 (Dec) 1934
- 10 Ellsworth R Studies on physiology of parathyroid glands action of parathyroid extract on renal threshold for phosphorus J Clin Investigation 11 1011 1017 (Sept) 1932
- 11 Ellsworth R and Howard J E Studies in physiology of the parathyroid glands VII Some responses of normal human kidneys and blood to intravenous parathyroid extract Bull Johns Hopkins Hosp 55 396 308 (Nov) 1934
- 12 Harrison H E and Harrison H C Renal excretion of inorganic phosphate in relation to action of vitamin D and parathyroid hormone J Clin Investigation 20 47 55 (Jan) 1941
- 13 Hunter D, and Aub J C Lead studies effect of parathyroid hormone on excretion of lead and of calcium in patients suffering from lead poisoning Quart J Med 20 123 140 (Jan) 1927
- 14 Ingalls T F Donaldson M A and Albright F Locus of action of parathyroid hormone experimental studies with parathyroid extract on normal and nephrectomized rats J Clin Investigation 22 603 608 (July) 1943
- 15 Jaffe H L Hyperparathyroidism (Recklinghausen's disease of bone) Arch Path 16 63 112 (July) 236 258 (Aug) 1933
- 16 Jaffe H L and Bodansky A Diagnostic significance of serum alkaline and acid phosphatase values in relation to bone disease Bull New York Acad Med 19 831 848 (Dec) 1943
- 17 Logan M A Early effects of parathyroid hormone on blood and urine J Biol Chem 127 711 719 (Mar) 1939
- 18 McChesney E W and Giacomino N J The treatment of experimental hypoparathyroidism in dogs J Clin Investigation 24 680 686 (Sept) 1945
- 19 Neufeld A H and Collip J B The primary action of the parathyroid hormone Endocrinology 30 135 141 (Jan) 1942
- 20 Reiss M Beiträge zur Wirkung des epithelkörperchenhormons Endokrinologie 2 161 169 (Sept) 1928
- 21 Selye H Mechanism of parathyroid hormone action Arch Path 34 625 632 (Oct) 1942
- 22 — Conference on Metabolic Aspects of Convalescence including Bone and Wound Healing 8th Meeting Oct 13 14 New York Josiah Macy Jr Foundation 1944 p 25
- 23 Short E Conference on Metabolic Aspects of Convalescence including Bone and Wound Healing 10th Meeting June New York Josiah Macy Jr Foundation 1944 p 160
- 24 Thomson D L and Collip J B Parathyroid glands Physiol Rev 12 309 383 (July) 1932
- 25 Tweedy W R Chilcote M E and Patras M C Distribution retention and excretion of radiophosphorus following thyroparathyroidectomy or bilateral nephrectomy and administration of parathyroid extract J Biol Chem 168 597 610 (May) 1947
- 26 Tweedy W R Smullen G H and Bell W P Action of acid and alkali on parathyroid hormone J Biol Chem 116 163 167 (Nov) 1936
- 27 Tweedy W R Templeton R D and Junkin F A Further studies on action of parathyroid extract in dog following total and partial ablation of kidneys Endocrinology 21 55 59 (Jan) 1937

C Parathyroidectomy

- 1 Albright F and Reifenstein M C Jr The Parathyroid Gland and Metabolic Bone Diseases p 34 Baltimore Williams & Wilkins 1948
- 2 Bodansky M and Duff V B Effects of parathyroid deficiency and calcium and phosphorus of diet on pregnant rats J Nutrition 21 119 192 (Feb) 1941
- 3 Bryan W R and Garrey W E Contributing factors in parathyroid tetany in dogs Arch

- über die Wirkung von Calcium und Natrium salze auf den Verlauf von experimenteller Tetanie *Neurol Centralbl* 26 1079 (Aug) 1907
- 46 Remak E Unter über die Entwicklung des Wirbelthieres Berlin Reimer 1855
 - 47 Salveus H A Studien on the physiology of the parathyroids *Acta med Scandinav Suppl* 6 1 160 19 3
 - 48 ——— Blutkalken under normale og rixte pathologische tilstande Norsk mag lægevidensk 20 1047 1052 (Dec) 1923
 - 49 Sandstrom I On a new gland in men and several mammals (glandulae parathyroideae) Upsala Lakareforeningens Forhandlingar 15 441 471 1879 1880 [*Bull Int Hist Med* 6 19 222 (Mar) 1938]
 - 50 Schlagenhauser Offizielles Protokoll der K. K. Wien Klin Wchnschr 28 1362 (Dec) 1915
 - 51 Stanski P G Du ramollissement des os en general et de celui du seuer Potiron en particulier Paris 1839
 - 52 Steenbock H Sell M T and Buell M V Fat soluble vitamins fat soluble vitamins and yellow pigmentation in animal fats with some observations on its stability to saponification *J Biol Chem* 47 89 109 (June) 1921
 - 53 Steenbock H and Nelson M T Fat soluble vitamins induction of calcifying properties in rickets producing ration by radiant energy *J Biol Chem* 62 209 216 (Nov) 1924
 - 54 Steinheim S L Zwei eltere Formen von hystischen Rheumatismus *Litt Ann d ges Heilk* Berlin 17 22 30 1850
 - 55 Trouseau A Clinique medicale de l'Hotel Dieu de Paris 2 117 114 1862
 - 56 Urechia C I and Popoviciu G Lergosterine irradiat dans la tetanie experimentale *Compt rend Soc de biol* 98 403-40 (Feb) 1928
 - 57 Vassale G and Generali F Sugh effetti dell estrazione della ghiandola paratiroidea *Riv di Pat Nerv e Ment Firenze* 1 95 99 1896
 - 58 Virchow R Die Krankhaften Geschwulste Vol 3 pt 1 p 13 Berlin Hirschwald 1864
 - 59 von Eiselsberg A F Ueber erfolgreiche Einheilung der Katzenhilddruse in die Bauchdecke und Austretung von Tetanie nach deren Exstirpation *Wien Klin Wchnschr* 5 81 85 (Feb) 1892
 - 60 von Recklinghausen F D Die Fibrose oder Deformierende Ostitis die Osteomalacie und die Osteoplastische Carcinose in ihren gegenseitigen Beziehungen (Festschrift f Rudolf Virchow) Berlin 1891
 - 61 Weil Medizinische Sektion der schlesischen Gesellschaft für vaterländische Kultur zu Breslau *Klin Wchnschr* 1 2114 1922
 - 62 Weiss N Ueber Tetanie *Klin Vortrage* (Vol 1) 1922 7 16 1 104 1880
 - 63 Welsh D A Concerning the parathyroid glands a critical anatomical and experimental study *J Anat & Physiol* 32 380 402 (Apr) 1898
 - 64 Windhaus A Linser O Luttinghaus A and Wudlich G Ueber das kristallisierte vitamin D *Ann Chem* 492 226 1932
 - 65 Cnallen A Sulle glandulae parathyroideae dell'uomo *Polichinica* 9 97 109 1907
 - 66 Erdheim J Zur normalen und pathologischen Histologie der Glandula thyroidea parathyroidea und Hypophysis *Beitr z path Anat u z allg Path* 33 158 236 1903
 - 67 Halsted W S and Evans H M The parathyroid glands their blood supply and their preservation in operation upon the thyroid gland *Ann Surg* 36 489 506 1907
 - 68 Johnstone G A and Voith Ostendorf F Thyroidectomy and the parathyroids *Arch Surg* 57 833 842 (Dec) 1948
 - 69 Kohn A Studien über die Schilddrüse *Arch f mikr Anat* 44 366 422 1895
 - 70 MacCallum W M The surgical relations of the parathyroid glands *Brit M J* 2 1282 1286 (Nov) 1906
 - 71 Ochsner A J and Thompson R L The Surgery and Pathology of the Thyroid and Parathyroid Glands pp 209 210 St Louis Mosby 1910
 - 72 Pappenheimer A M. and Widens E L Enlargement of the parathyroid glands in renal disease *Am J Path* 11 73 91 (Jan) 1935
 - 73 Peperce A Le glandoi paratiroidee Ricerche anatomiche e sperimentali Torino 1906
 - 74 Pool E H and Falk H C Concerning the surgical anatomy of the thyroid with special reference to the parathyroid glands, *Ann Surg* 63 11 77 (Jan) 1916
 - 75 Schaeffer J P Morris Human Anatomy ed 10 p 1493 Philadelphia Blakiston 1942
 - 76 Welsh D A Concerning the parathyroid gland a critical anatomical and experimental study *J Anat & Physiol* 32 380-402 (Apr) 1898

III EMBRYOLOGY

- 1 Aray L B Developmental Anatomy ed 3 p 192 Philadelphia Saunders 1916
- 2 Aspuru C E and Black B M Embryologic considerations in surgery of neck Mediastinal adenoma of parathyroid gland report of case *Proc Staff Meet Mayo Clin* 37 61 (Feb) 1947
- 3 Norris E H The parathyroid glands and the lateral thyroid in man their morphogenesis histogenesis topographic anatomy and prenatal growth *Contrib Embryol* 26 1937
- 4 Weller G L Development of the thyroid parathyroid and thymus glands in man *Contrib Embryol* 24 93 139 (Sept) 1933

IV CONGENITAL ANOMALIES

- 1 Abrams M Kutenberg A M Jesses M F and Gargel S L Hyperparathyroidism and nephrolithiasis *New England J Med* 241 401-406 (Sept) 1949
- 2 Halsted W M and Evan H M The parathyroid glands their blood supply and their preservation in operation upon the thyroid gland *Ann Surg* 46 489 506 (Oct) 1907
- 3 Hembach W F Jr A study of the number and location of the parathyroid glands in man *Anat Rec* 57 251 257 (Oct) 1933
- 4 Ochsner A J and Thompson R L The Surgery and Pathology of the Thyroid and Parathyroid Glands pp 212 220 St Louis Mosby 1910

II ANATOMY

- 1 Bet C H and Taylor N B Physiological Basis of Medical Practice ed 4 700 Baltimore Williams & Wilkins 1945

VIII BIO ASSAY

- 1 Collip J B Extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates level of blood calcium *J Biol Chem* 63 395 438 (Mar) 1925
- 2 Thomson H L and Collip J B The parathyroid glands *Physiol Rev* 12 309 384 (July) 1932

IX PATHOLOGY

- 1 Albright F Drake T G and Sulkowitch H W Renal osteitis fibrosa cystica report of a case with discussion of metabolic aspects *Bull Johns Hopkins Hosp* 60 377 399 (June) 1937
- 2 Albright F Bloomberg E Castleman B and Churchill E D Hyperparathyroidism due to diffuse hyperplasia of all parathyroid glands rather than adenoma of one clinical studies on 3 such cases *Arch Int Med* 54 315 329 (Sept) 1934
- 3 Albright F Burnett C H Smith P H and Parson W Pseudo hypoparathyroidism—example of Seabright bantam syndrome report of 3 cases *Endocrinology* 30 922 932 (June) 1942
- 4 Alexander H H Kepler E J Pemberton J deJ and Broders A C Functional parathyroid tumors and hyperparathyroidism *Am J Surg* 65 157 188 (Aug) 1943
- 5 Bennet G A Bauer W and Albright F in Albright F and Reifenstein E C Jr The Parathyroid Glands and Metabolic Bone Diseases pp 111 112 Baltimore Williams & Wilkins 1948
- 6 Castleman B and Mallory T B The pathology of the parathyroid gland in hyperparathyroidism study of 25 cases *Am J Path* 11 1 72 (Jan) 1935
- 7 Cope O Endocrine aspect of enlargements of parathyroid glands *Surgery* 16 273 288 (Aug) 1944
- 8 Drake T G Albright F Bauer W and Castleman B Chronic idiopathic hypoparathyroidism report of six cases with autopsy findings in one *Ann Int Med* 12 1751 1765 (May) 1939
- 9 Erdheim J Zur Kenntnis der parathyreoipriven Dentin Veränderung Frankfurt Ztschr f Path 7 238 248 1911
- 10 Erdheim J and Albright F in Albright F and Reifenstein E C Jr The Parathyroid Glands and Metabolic Bone Diseases p 31 Baltimore Williams & Wilkins 1948
- 11 *Ibid* pp 77 79
- 12 Fretheim H and Lange H F Carcinoma of parathyroid with hyperparathyroidism *Acta endocrinol* 1 203 216 1948
- 13 Jaffe H L Hyperparathyroidism (Reckling

- hausen's Disease of Bone) *Arch Path* 11 66 112 (July) 236 258 (Aug) 1933
- 14 Norris E H Collective review carcinoma of parathyroid glands with a preliminary report of 3 cases *Internat Abstr Surg* 86 1 21 (Jan) 1948
- 15 Ochsner A J and Thompson R L The Surgery and Pathology of the Thyroid and Parathyroid Glands pp 243 280 St Louis Mosby 1910
- 16 Rogers M M Parathyroid adenoma and hypertrophy of parathyroid glands *JAMA* 130 22 28 (Jan) 1946
- 17 Stephenson H U Jr Malignant tumors of the parathyroid glands *Arch Surg* 60 247 266 (Feb) 1950
- 18 Young J H and Emerson K Jr Parathyroid carcinoma associated with acute parathyroid intoxication *Ann Int Med* 30 823 837 (Apr) 1949
- 19 Warren S and Morgan J R E Parathyroid glands, histologic study of parathyroid adenoma *Arch Path* 20 823 835 (Dec) 1935

XIII EXAMINATION OF PATIENT

- 1 Albright F and Reifenstein E C Jr The Parathyroid Glands and Metabolic Bone Diseases pp 31 32 Baltimore Williams & Wilkins 1948
- 2 *Ibid* pp 260 262
- 3 Barney J D and Sulkowitch H W Progress in the management of urinary calculi *J Urol* 37 746 762 (June) 1937
- 4 Ellsworth R and Howard J E Studies on physiology of parathyroid glands some responses of normal human kidneys and blood to intravenous parathyroid extract *Bull Johns Hopkins Hosp* 55 296 308 (Nov) 1934
- 5 Emerson K Jr and Beckman W U Calcium metabolism in nephrosis I A description of an abnormality of calcium metabolism in children with nephrosis *J Clin Investigation* 24 564 572 (July) 1945
- 6 Gilligan D R Volk M C and Gargill B L Experience with Hamilton and Highman test for parathyroid hyperfunction in chronic nephritis, toxic goiter and Paget's disease of bone *J Clin Investigation* 17 641 647 (Sept) 1938
- 7 Hamilton B L K and Schwartz C A method for the determination of small amounts of parathyroid hormone *J Pharmacol* 6 285 292 (Nov) 1937
- 8 Hamilton B and Highman W J Test for abnormally large amounts of parathyroid hormone in blood *J Clin Investigation* 15 99 100 (Jan) 1936
- 9 Winer N J The Hamilton Schwartz test and hyperparathyroidism in various diseases *Am J M Sc* 202 642 650 (Nov) 1941

- temperature panting and overventilation *Am J Physiol* 96 194 208 (Sept.) 1931
- 4 Chandler S B Relation of parathyroidectomy to estrus pregnancy and lactation in albino rat *Anat Rec* 83 105 120 (July) 1932
 - 5 Collip J B The Parathyroid Glands Harvey Lect (1925 1926) 21 113 172 1926
 - 6 Erdheim J Ueber tetania parathyroprivia *Wien Klin Wchnschr* 19 716 717 1906
 - 7 — Tetania parathyroprivia Mitt a d Grenzgeb d Med u Chir 16 632 744 1906
 - 8 — Zur Kenntnis der parathyroprivien *Dentist Veränderung Frankf Ztschr f Path* 7 238 249 1911
 - 9 Greenwald I The effect of parathyroidectomy upon metabolism *Am J Physiol* 103 137 1911
 - 10 — Effect of administration of calcium salts and of sodium phosphate upon calcium and phosphorus metabolism of thyroparathyroidectomized dogs with consideration of nature of calcium compounds of blood and their relation to pathogenesis of tetany *J Biol Chem* 67 1 28 (Jan) 1926
 - 11 Greep R O The physiology and chemistry of the parathyroid hormone in Pincus G and Thimann R V The Hormones Vol 1 pp 259 265 New York Acad Press 1943
 - 12 Grollman A Essentials of Endocrinology ed 2 p 252 Philadelphia Lippincott 1947
 - 13 Hursthal L M Unpublished data
 - 14 Jung F T and Shillen W G Effects of thyroparathyroidectomy on the teeth of the rat *Proc Soc Exper Biol & Med* 26 598 600 (Apr) 1929
 - 15 MacCallum W C and Vortexin C On the relation of the parathyroid gland to calcium metabolism and to tetany *J Exper Med* 11 118 151 1907
 - 16 Pope A and Aub J C Medical progress parathyroid glands and parathormone *New England J Med* 230 693 707 (June) 1944
 - 17 Salvesen H A Studies on the physiology of the parathyroids *Acta med Scandinav Suppl* 6 pp 1 149 1923
 - 18 Thomson M L and Collip J B The parathyroid glands *Physiol Rev* 12 309 383 (July) 1932
- II Hyperhormonal Effects**
- 1 Collip J B The Parathyroid Glands Harvey Lect (1925 1926) 21 113 172 1926
 - 2 de Robertis E Cytology of parathyroid gland of rats given injections of parathyroid extract *Anat Rec* 78 473 495 (Dec) 1940
 - 3 Greenwald I and Gross J The effect of the administration of a potent parathyroid extract upon the excretion of nitrogen phosphorus calcium and magnesium with some remarks on the solubility of calcium phosphate in serum and on the pathogenesis of tetany *J Biol Chem* 66 217 227 (Nov) 19 5
 - 4 — The effect of long continued administration of parathyroid extract upon excretion of phosphorus and calcium *J Biol Chem* 68 325 333 (May) 1926
 - 5 Grollman A Condition of inorganic phosphorus of blood with special reference to calcium concentration *J Biol Chem* 72 565 572 (Apr) 19 1
 - 6 Hueper W Metastatic calcifications in the organs of the dog after injections of parathyroid extract *Arch Path* 3 14 25 (Jan) 1927
 - 7 — Effect of repeated injections of parathyroid extract on calcification of osteoid tissues *Arch Path & Lab Med* 3 1007 1007 1927
 - 8 Jaffe H L Bodansky A and Blair J E Fibrous osteodystrophy (osteitis fibrosa) in experimental hyperparathyroidism of guinea pigs *Arch Path* 11 07 728 (Feb) 1931
 - 9 Jaffe H L and Bodansky A Diagnostic significance of serum alkaline and acid phosphatase values in relation to bone disease *Bull New York Acad Med* 19 841 848 (Dec) 1943
 - 10 McLean F C and Bloom W Calcification and ossification mobilization of bone salt by parathyroid extract *Arch Path* 32 315 333 (Sept.) 1941
 - 11 Pope A and Aub J C The parathyroid glands and parathormone *New England J Med* 230 693 707 (June) 1944
 - 12 Selve H Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 5th Meeting Oct 13 14 New York Josiah Macy Jr Foundation 1944 p 25
 - 13 — Textbook of Endocrinology *Acta Endocrinologica Montreal Universite de Montreal* 1947 p 357
 - 14 Thomson D L and Collip J B Parathyroid gland *Physiol Rev* 12 309 383 (July) 1932
- E Histophysiology**
- 1 Castleman B and Mallory T B The pathology of the parathyroid gland in hyperparathyroidism study of 25 cases *Am J Path* 11 1 7 (Jan) 1935
 - 2 Dempsey E W Chemical Cytology of Endocrine Glands Recent Progress in Hormonal Research New York Acad Press 1943 Vol 1 11 133
- F Activity at Different Periods in Life**
- 1 Bodansky M and Duff V B Regulation of level of calcium in serum during pregnancy *JAMA* 112 223 229 (Jan) 1939
 - 2 Castleman B and Mallory T B The pathology of the parathyroid gland in hyperparathyroidism study of 25 cases *Am J Path* 11 1 72 (Jan) 1935
 - 3 Norris H H Anatomical evidence of prenatal function of the human parathyroid glands *Anat Rec* 96 129 142 (Oct) 1946
- VII CHEMISTRY**
- 1 Collip J B and Clark F P Further studies on physiological action of parathyroid hormone *J Biol Chem* 64 485 507 (June) 1925
 - 2 — Parathyroid hormone *J Biol Chem* 66 133 137 (Nov) 1925
 - 3 Greep R O The physiology and chemistry of the parathyroid hormone in Pincus G and Thimann R V The Hormones Vol 1 pp 274 2 6 New York Acad Press 1943
 - 4 Hanson A M An elementary chemical study of the parathyroid glands of cattle *Mil Surg* 52 280 81 (Mar) 19 3
 - 5 Ross W F. and Wood T R Partial purification and some observations on nature of parathyroid hormone *J Biol Chem* 146 49 58 (Nov) 1942

SECTION 37

PRIMARY HYPOPARATHYROIDISM

SYNONYMS Aparathyrosis, Hypoparathyrosis

I DEFINITION

A state caused by a deficient or absent secretion of the parathyroid glands which when of a sufficient degree results in tetany (Tetany is characterized by hyperexcitability of the nervous system, intermittent painful spasms of the muscles, and is not always due to hypoparathyroidism)

II APPEARANCE

Aside from the rare occurrence of patchy alopecia of head hair, cataracts and carpopedal spasm on effort, a patient with chronic hypoparathyroidism may present no special characteristics

III AGE

All also reported in newborn¹¹

A POSTOPERATIVE TYPE

Seen more frequently in adult females because greater incidence of thyroid disease

B IDIOPATHIC TYPE

Childhood, adolescence and after 40

IV SEX

Both females predominate

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal

B RESPONSIVENESS

Slow when depressed

C OTHER ABNORMALITIES

Marked dejection in some cases, dementia, mania and psychoses reported^{12 17 7 31 54 71}

VI PHYSICAL STATUS

A NUTRITION

Normal

1 Weight

Decreased occasionally

2 Fat distribution

Normal

B HEIGHT

May be retarded in children

C EXTREMITIES (see 37 VII M)

1 Upper

Normal

a Hands

Normal

b Fingers

Normal

c Span

Normal

2 Lower

Normal

a Feet

Normal

b Toes

Normal

D SPINE

Normal

E INTEGUMENT

1 General

Normal or may be rough scaly hyperkeratotic

a Texture

Normal

b Temperature

May be absent

c Moisture



FIG 235 NORMAL PARATHYROID GLAND
Note sinusoidal arrangement of cells i.e.
cords of cells with capillaries between them
(x 13)

L GENITALIA**1 Male**

- a Penis Normal
- b Testes Normal
- c Prostate Normal

2 Female

- a External Normal
- b Internal Normal

M NEUROMUSCULAR**1 Muscles**

Gro shv normal but hyperirritable, especially on exertion

- a Positive Chvostek's sign (see 36 VIII A 2 d (1)) when untreated or insufficiently treated in rare cases (see Protocol 37, XXV) hyperirritability may not be demonstrated clinically except possibly by Erb's sign (see 36 VIII A 2 d (3))
- b Carpopedal spasm may be present at rest or on effort in subacute or chronic untreated stage, or elicited by Trousseau's sign (see 36 VIII A 2 d (2), Fig 241)
- c Abdominal muscles may be rigid with acute tetany
- d Spasm of anal sphincter^a
 - Isolated muscular twitchings may occur
- f Opisthotonos occasionally in children
- g See characteristics of acute tetany (see 37 VII A)

2 Gait

May be hampered by muscular spasm in severe cases

3 Body movements

Characteristic stance with sudden motion in some severe cases arms and few fingers are flexed or extended with slow athetoid movements

4 Tremor

None

5 Paresthesias

About lips, side of face and in extremities with or without active spasm, the latter indicating a very mild or latent state

6 Reflexes

Normal absent or increased

7 Petit mal attacks and convulsive seizures (see 37 VII A B)**N SPEECH**

Normal unless laryngeal spasm

VII LABORATORY DATA**A URINE****1 General**

Normal

2 Special analyses

- a Sugar Normal
- b Albumin Normal
- c Nitrogen No data
- d Creatine No data
- Creatinine No data
- f Sodium No data
- g Potassium Normal
- h Calcium Decreased negative Sulkowitch test if serum calcium is below normal threshold (see Chart 140 p 1474)
- i Phosphorus Decreased
- j Chloride No data
- k Iodine Normal^{1a}

B HEMATOLOGY

- 1 Red blood cells Normal
- 2 Hemoglobin Normal
- 3 White blood cells Normal
- 4 Differential Normal

d Eruptions	Secondary to vitamin deficiencies, impetigo herpetiformis ⁴²
■ Pigmentation	Normal
f Color	Normal
g Nails ^{7 41 54}	All may be affected hypoplastic deformed pitted, grooved ridged irregular may be seat of Monilia infection, in which case each one is not involved, transverse grooving may appear with treatment (see Fig 239)
2 Hair ^{2 3 41 43}	
a Head	Patchy or total alopecia is rare premature graying
b Facial	May lose eyebrows and eyelashes
■ Axillary	May be absent
d Pubic	May be absent
■ Body	Normal
F HEAD	
1 Shape and size	Normal
2 Facial expression	Often dull
3 Eyes	
a General	Photophobia lacrimation (rare) ⁴⁰ keratoconjunctivitis, zonular or central cataracts are found (slit lamp may be necessary to detect these) ³⁴ may have diplopia
b Fundi	Normal optic edema or hemorrhage ^{1 35}
c Visual	
(1) Fields	Normal
(2) Acuity	Decreased with optic edema or cataracts
4 Ears and nose	Normal
5 Mouth and throat	
a General	Normal tongue and mucous membranes may show Monilia infection (see 36 I\ B 3) rhagades seen from secondary vitamin B deficiency (see Protocol 37, XVI)
b Teeth	Enamel defects ²⁹ transverse pitting occurs only during development but persists
c Larynx (voice)	Normal or may have indistinct speech during active tetany aphonia with chronic laryngeal spasm
G NECK	
1 General	Often thyroidectomy scar
2 Thyroid	Normal absent or goiter in India
H CHEST	Normal unless complications (see 37 VIII F 1)
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal may have beriberi heart
2 Rate and rhythm	Normal or increased rate
3 Blood pressure	Normal
4 Peripheral arteries and veins	Normal
5 Vasomotor	Normal
J BREASTS	
1 Male	Normal
2 Female	Normal
K ABDOMEN	
1 Liver	Normal unless congestive heart failure (see Protocol 37 XVI)
2 Spleen	Normal
3 Hernia	None
4 Tumor	None

G BIOPSY

- | | |
|---------------|---------|
| 1 Endometrial | No data |
| 2 Testicular | No data |

H VAGINAL SMEAR

No data

I SEMEN ANALYSIS

No data

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL

- | | |
|-----------------|--|
| 1 Cranial vault | Calcification in region of anterior horns and basal ganglia (see Fig 243) ²² = 61 |
| 2 Sella turcica | Normal |
| 3 Sinuses | Normal |
| 4 Mandible | Normal |
| 5 Teeth | Blunted roots if onset is during development ⁶ 7 |

II EPIPHYSEAL STATUS (bone age)

May be retarded if onset is during development

C LONG BONES

Normal or occasionally dense (see 37 VI)⁵ 4

D VERTEBRAE

Normal

E BONE TEXTURE

Normal, occasionally increased density, ³ 4 rarely osteomalacia in childhood

F MISCELLANEOUS

1 Chest

Heart may be enlarged, may be fluid (see Fig 244)

IX ETIOLOGY

A SURGICAL

- 1 Removal of parathyroid glands due to hyperactivity
- 2 Following subtotal thyroidectomy⁴³ 43

B CONGENITAL OR FAMILIAL⁴³ 43

- 1 Aplasia
- 2 Transient neonatal hypofunction¹²
- 3 Moniliasis infection may be ⁹ 61
 - a Cause since it usually precedes hypoparathyroidism
 - b Associated disease

C INFARCT

D IDIOPATHIC¹⁰ 1 43 6- 70

E INFECTIONS

- 1 Syphilis
- 2 Tuberculosis
- 3 Measles
- 4 Otitis media
- 5 Influenza

F NONREACTIVITY OF END ORGANS TO PARATHYROID HORMONE (pseudohypoparathyroidism)

3 Fatty tissue

4 Cysts

B MICROSCOPIC

1 Parathyroids

- a Normal tissue in pseudohypoparathyroidism⁵
- b Hemorrhages observed in infantile tetany
- c Atrophy
 - (1) Epithelial elements may be completely absent
 - (2) Fat globules
 - (3) Capsule and blood supply may remain

d Cysts

- (1) Number—none to several
- (2) Size
 - (a) Variable
 - (b) Some are 3 to 6 cm in diameter

e Fibrosis

f Inflammation from surrounding area

g Fatty degeneration²¹h Hypoplasia¹2 Pituitary—increased or absence of basophils has been reported¹ 46

3 Adrenals

- a Involvement rarely
- b Absence of cortex⁴⁹
- c Tuberculosis probable

X PATHOLOGY

A GROSS—Parathyroids

- 1 Normal
- 2 Atrophy¹³

C BLOOD CHEMICAL ANALYSES

1 Sugar	Normal
2 Nonprotein nitrogen	Normal
3 I rotein	
a Albumin	Normal or increased slightly
b Globulin	Normal or increased lightly
c A/G ratio	Normal
4 Uric acid	Normal or decreased
5 Cholesterol	Normal unless thyroid deficiency is also present then increased
6 Sodium	May be increased
7 Potassium	May be low in idiopathic type ²⁷
8 Calcium	Usually below 9 mg % (see Charts 79 and 82)
9 Phosphorus	Commonly above 4.0 mg %
10 Phosphata e	Usually low decreased to 2 Bu in adults or 5 Bu in children
11 Chlorides	Normal or increased
12 Iodine	Normal ¹⁹
13 Creatine	No data
14 Magnesium	Decreased

D FUNCTION TESTS

1 Tolerance	
a Glucose	Normal
b Glucose insulin	No data
c Insulin	No data
2 Adrenal water test	Reported positive ⁴
3 Salt deprivation	No data (see 37 XIV)
4 Balance	
a Nitrogen	Normal

E MISCELLANEOUS TESTS

1 Basal metabolic rate	Normal
2 Circulation time	Normal
3 Sedimentation rate	May be increased
4 Specific dynamic action of protein	No data normal probably
5 Gastric analysis	Hydrochloric acid is increased or absent ⁶⁴
6 Electrocardiogram	QT interval may increase from 0.30 (normal) to 0.67 sec also changes in T waves (see Fig 242) ^{3 30 41 59 64 66}
7 Spinal fluid	Normal or increased pressure ¹¹
8 Electroencephalogram	Alpha rhythm in occipital parietal and frontal area tend to disappear increase in beta rhythm in striking groups of 6 to 1 slow waves 2 to 3/sec treatment corrects but hyperventilation will again evoke changes in some cases ^{43 44 64 66}

F URINARY HORMONE ASSAYS

1 FSH	Insufficient data (see 37 XII II 7) ⁴³
2 LH	No data
3 Estrogens	Normal or low (see 37 XII II 7) ⁴³
4 Pregnanediol	No data
5 17 keto steroids	No data
6 11-oxy steroids	No data
7 Aschheim Zondek	No data negative probably
8 TSH	No data normal variations

- decrease in ionized calcium of the tissues which is necessary to maintain normal function of nerves and tissues
- 2 The mechanism of this is unknown since tetany occurs under a variety of conditions in which the calcium or phosphorus content of tissue (extra cellular and intracellular) fluids cannot be determined
- 3 Tetany may be found with serum levels as follows
 - Normal calcium and phosphorus with alkalization of blood
 - b Normal calcium and high phosphorus
 - c Low calcium and high phosphorus
 - d Low calcium and low phosphorus
- 4 In hypoparathyroidism
 - Tissue fluids are certainly not saturated with calcium, although it is often deposited in cells (?) (i.e., cataracts, brain)
 - b However there is failure to calcify dentine and possibly bone during the growth period
- 5 Potassium depletion may prevent tetanic manifestations even with low serum calcium value
- 6 Many factors in tetany are still obviously obscure
 - (2) Transverse wrinkling of forehead
 - e Larynx
 - (1) Characteristic loud inspiratory crow
 - (2) Spasm may last minutes to hours
 - d Extremities (see Fig 240)
 - (1) Unilateral or bilateral involvement
 - (2) Carpal spasm ("obstetric hand"), may start on right side, if right handed
 - (3) Pedal spasm
 - (4) Adductor muscles of thighs may be affected
- 4 Deep reflexes may be increased
- 5 Convulsive seizures¹⁶
 - a Epileptiform in many details and are mistaken for it
 - b Duration—a few seconds to hours
 - c Attack may start in hands and spread over whole body
 - d Any of the following may be observed
 - (1) Loss of consciousness
 - (2) Facial contractions producing distorted and freakish expressions
 - (3) Strabismus
 - (4) Inequality of pupils
 - (5) Nystagmus
 - (6) Chin may touch sternum
 - (7) Thick speech if conscious
 - (8) Biting of tongue
 - (9) Frothing at the mouth
 - (10) Difficulty swallowing
 - (11) Involvement of all smooth muscles
 - (12) Diaphragmatic spasm
 - (13) Cyanosis
 - (14) Severe cramplike pain in any or all muscles
 - (a) Tonic or clonic contractions
 - (b) Unilateral or bilateral
 - (c) Upper lower or all groups
 - (15) Spasm of heart muscle causing death
 - (16) Opisthotonos in children
 - e Deep sleep may follow
- 6 Mental symptoms
 - a Depression
 - b Anxiety

XII SYMPTOMATOLOGY

A ACUTE HYPOPARATHYROIDISM WITH TETANY

- 1 Introduction
 - a Acute hypoparathyroidism gives rise to tetany but the latter may also be caused by other disturbances
 - b The following signs and symptoms are not pathognomonic of acute hypoparathyroidism only
 - c Acute tetany may occur periodically in chronic hypoparathyroidism
- 2 Numbness and tingling of
 - Upper lip
 - b Side of face
 - c Extremities
- 3 Contractions of
 - Eyelids (blephorospasm)
 - b Facial muscles
 - (1) Corners of mouth may be drawn ('carp mouth') down with projection of nasolabial fold

- 4 Thymus
 - a Normal
 - b Scant¹
 - c Hyperplastic¹
- 5 Brain
 - a Normal
 - b Calcification of²²
 - (1) Arteries
 - (2) Basal ganglia

XI PATHOLOGIC PHYSIOLOGY

A LOSS OF PARATHYROID HORMONE^{3 37 38}

- 1 Phosphate retention
- 2 Calcium in serum and extracellular fluid = low (see 36 VI B)
- 3 Absorption of calcium and all vitamins is poor
- 4 Osteoclastic activity is retarded causing decreased formation of osteoblasts
- 5 Ectodermal changes
- 6 Central nervous system alterations and convulsive seizures may be due to increased intracranial
 - a Fluid content
 - b Pressure

B PHYSICOCHEMICAL ALTERATIONS ASSOCIATED WITH TETANY

- 1 High serum phosphate (excess phosphate retention) with normal serum calcium may be produced in
 - a Animals with phosphate injections
 - b Newborns whose parathyroid function is inadequate and if cow's milk (excess phosphate) is given
- 2 Low serum calcium with
 - a High serum phosphorus (usual)
 - b Low serum phosphorus as in acute tetany after removal of parathyroid adenoma (see 38 VI)
- 3 Alkalosis from
 - a Increased consumption of sodium bicarbonate especially with poor renal function
 - b Overventilation can change reaction of blood from pH 7.4 to pH 7.9
 - c Excess vomiting and loss of hydrochloric acid producing an increase in
 - (1) Carbon dioxide combining power
 - (2) pH
- 4 Combined forms 3 a or 3 b alone or with 3 c
- 5 Factors aggravating existent parathyroid tetany (latent or manifest)

- a Alkalosis (see above)
- b High serum potassium
- c Menstruation questionable relationship to sodium retention
- d Pregnancy
- e Lactation
- f High phosphorus intake
- g Sodium citrate
- h Avitaminosis D
 - i Mercurial diuretics¹
- j Acute infections
- k Exercise
- l Emotion
- m Vomiting
- n Diarrhea
- o Cessation of medication in controlled tetany

6 Factors ameliorating parathyroid tetany (manifest or latent)—see Chart 78

- a Acid salts
- b Ferrous ammonium citrate
- c Calcium intravenous or oral
- d Dihydrotachysterol
- e Vitamin D
- f Parathyroid hormone
- g Curare
- h Carbon dioxide inhalation questionable
 - i Low serum potassium

7 Factors aggravating tetany of nonparathyroid origin

- a Alkalosis producing agents
 - (1) Sodium bicarbonate
 - (2) Sodium citrate possibly
- b Alkalosis producing disorders
 - (1) Pyloric obstruction with vomiting
 - (2) Emphysema
- c Renal insufficiency on account of phosphate retention
- d Menstruation
- e Pregnancy
- f High serum potassium

8 Factors tending to ameliorate manifest tetany from any cause

- a Acid salts
- b Calcium intravenously
- c Carbon dioxide inhalation
- d Low serum potassium

C MECHANISM OF TETANY

- 1 Theory—a decrease in ionized calcium in serum from any physicochemical alteration mentioned above produces

- (2) Exception after removal of parathyroid adenoma with high alkaline phosphatase may remain low

B PRIMARY HYPOPARATHYROIDISM WITHOUT MANIFEST OR LATENT TETANY

- 1 History is not very significant
- 2 Symptomatology
 - a None
 - b Failing vision
- 3 Physical status (see 37 VI)
 - No abnormalities
 - b Cataracts
 - Chvostek's and Trousseau's signs may be negative
- 4 Blood chemical analyses
 - a Calcium (serum) may be as low as 6 mg %
 - b Phosphorus (serum) may reach 5 mg %

C CHRONIC HYPOPARATHYROID TETANY

- 1 History
 - a Subtotal thyroidectomy — delayed tetany may be due to gradual loss of blood supply to parathyroids
 - b Operation for cataracts, especially in younger age group
- 2 Symptomatology—see 37 VII
- 3 Physical status
 - a Cataracts or evidence of previous iridectomy
 - b The following signs are positive (see 36 VIII)
 - (1) Chvostek, not pathognomonic
 - (2) Trousseau, may not be characteristically elicited
 - (3) Erb
 - (4) Pool
 - (5) Schlesinger
 - (6) Lust
- 4 Laboratory data
 - a Sulkowitch test is negative if serum calcium is below 7 to 8.5 mg %
 - b Calcium (serum)
 - (1) Is rarely if ever below 4.5 mg %
 - (2) May be only slightly decreased especially if serum phosphorus is high
 - c Phosphorus (serum)
 - (1) Is rarely below 4 mg %
 - (2) May reach 16 mg % or more (see Chart 81)

XIV DIFFERENTIAL DIAGNOSIS

A DISORDERS WITHOUT TETANY

The following are excluded as being the result of hypoparathyroidism when normal serum calcium and phosphorus values are present

- 1 Cataracts
- 2 Mental depression or psychoses
- 3 Diarrhea
- 4 Ectodermal defects
- 5 Vitamin deficiencies

B CONDITIONS WITH TETANY (latent or manifest)

- 1 Tetanus
 - a Characteristics
 - (1) Risus sardonius
 - (2) Lockjaw
 - (3) Rigidity of muscles
 - (4) Opisthotonos
 - (5) Tonic convulsive seizures
 - (6) Deep reflexes are hyperactive
 - (7) Profuse sweating
 - (8) Sensorium is perfectly clear
 - (9) Exhaustion
 - b Laboratory data
 - (1) Sulkowitch test—normal
 - (2) Normal serum
 - (a) Calcium
 - (b) Phosphorus

2 Avitaminosis D

- a Occurrence
 - (1) Rickets
 - (2) Spasmophilia
 - (3) Osteomalacia
- b Characteristics
 - (1) Skin lesions
 - (2) Cataracts are absent
 - (3) Signs of tetany may be present
 - (4) Bone deformities as in rickets
- c Laboratory data
 - (1) Calcium (serum)
 - (a) Normal — normocalcemic hypophosphatemic type
 - (b) Decreased — hypocalcemic normophosphatemic type
 - (2) Phosphorus (serum) (see above)
 - (a) Normal
 - (b) Decreased
 - (3) Alkaline phosphatase (serum) — may be increased
- d Roentgenographic findings — osteomalacia (see Fig 259, p 635)

- c Irritability
- d Dullness
- e Hallucinations
- f Loss of memory
- g Disorientation

II CHRONIC HYPOPARATHYROIDISM^{5 1 14 1}

- 1 Tetany may be
 - a Absent
 - b Latent—asymptomatic except under aggravating circumstances
 - Manifest—mild or moderate symptoms present constantly
 - d Acute—occurs in b or c under special circumstances
- 2 Neuromuscular
 - a Headache
 - b Visual disturbances
 - c Petit mal
 - d Mental changes
 - (1) Anxiety
 - (2) Depression
 - (3) Dementia
 - e Neurogenic bladder
 - f Paresthesias
- 3 Ectodermal
 - a Alopecia^{77 35 44 45}
 - b Skin—dry
 - c Nail growth retarded
 - d Dental defects (during growth period)
 - e Cataracts⁴
- 4 Gastro intestinal
 - a Anorexia
 - b Diarrhea
 - c Constipation
- 5 Vitamin deficiencies
 - a Sore tongue
 - b Rhagades
 - c Cheilosis
 - d Tachycardia
 - e Dyspnea
 - f Edema
 - Hemorrhagic tendency
- 6 Growth may be delayed
- 7 Sexual function
 - Genital development may be retarded
 - b Amenorrhea
 - Loss of libido in males

XIII DIAGNOSIS

A PRIMARY HYPOPARATHYROIDISM WITH ACUTE TETANY

- 1 Occurrence to be watched for following
 - a Subtotal thyroidectomy
 - b Partial resection of hyperplastic parathyroids
 - c Removal of parathyroid adenomas
- 2 Symptomatology
 - a Onset may be
 - (1) Severe and sudden
 - (2) Mild with only
 - (a) Numbness
 - (b) Tingling
 - (3) Without symptoms, except for positive signs of
 - (a) Chvostek
 - (b) Trousseau
 - b Tingling or numbness of
 - (1) Face
 - (2) Lips
 - (3) Extremities
 - c Mental
 - (1) Depression
 - (2) Great anxiety
- 3 Physical status
 - a Chvostek's sign
 - (1) Positive
 - (2) Early finding but not always pathognomonic
 - b Trousseau's sign
 - (1) Positive
 - (2) Negative
 - c Carpopedal spasm
 - d Laryngeal spasm must be differentiated from
 - (1) Bilateral cord paralysis
 - (2) Pressure on trachea from post operative
 - (a) Hemorrhage
 - (b) Edema
 - (3) Croup
 - (4) Diphtheria
 - Convulsive seizures with or without unconsciousness
- 4 Blood chemical analyses
 - a Calcium (serum)
 - (1) Rarely if ever below 4.5 mg %
 - (2) Usually below 8 mg %
 - b Phosphorus (serum)
 - (1) Above 4 mg %

- (5) Blood pressure
 - (a) Normal
 - (b) Elevated
- (6) Genito urinary pathology
 - (a) Polycystic kidneys
 - (b) Congenital urinary obstruction
- (7) Osteoporosis may be absent
- Laboratory data
 - (1) Urine
 - (a) Albumin—variable amounts
 - (b) Sulkowitch test—negative
 - (2) Nonprotein nitrogen (blood)—increased
 - (3) Calcium (serum)—low, 5 to 7 mg %
 - (4) Phosphorus (serum)—high, 10 to 20 mg %
 - (5) Phenolsulfonphthalein test—decreased renal function

C CHRONIC NEPHRITIS

- 1 Characteristics
 - a Tetany signs are rare (see Protocol 37, \XVII)
 - b Compensating parathyroid hyperplasia and acidosis usually counteract
 - (1) Phosphorus retention
 - (2) Hypocalcemia
- 2 Laboratory data
 - a Urine—evidence of chronic nephritis
 - b Nonprotein nitrogen (blood)—elevated
 - c Calcium (serum)—may be
 - (1) Normal
 - (2) Low
 - (3) Elevated
 - d Phosphorus (serum)—increased
- 3 Roentgenographic finding—osteoporosis if disease of sufficient duration

D NEPHROSIS^o

- 1 Characteristics
 - Tetany—absent (ionized or diffusible calcium is normal)
 - b Growth—normal
- 2 Laboratory data
 - Urine
 - (1) Albumin—markedly increased
 - (2) Calcium—decreased
 - b Cholesterol (plasma)—increased
 - c Calcium (serum)—low due to decreased serum protein
 - d Phosphorus (serum)—variable

- Phosphatase (serum)—normal
- f Fecal calcium excretion—increased
- 3 Roentgenographic findings—long bone shafts show slight decalcification cause
 - obscure

E EPILEPSY

- 1 Occurrence
 - a Idiopathic
 - b Brain tumor
 - Other intracranial lesions
- 2 Characteristics
 - a No signs of tetany (except possibly from overbreathing in some cases)
 - b Epilepsy may be
 - (1) Coexistent with hypoparathyroidism
 - (2) Aggravated by tetany
 - c Aura—present
 - d Evidence of tongue bite are often present
 - e Unconsciousness in grand mal
 - f Loss of sphincter control
 - g Unilateral contractures
 - h Opisthotonos—absent
 - i Choked disks may be present (also in tetany)
- 3 Laboratory data
 - a Calcium and phosphorus (serum)—normal
 - b Electroencephalogram (see 37 VII E 8)
 - (1) Normal
 - (2) Abnormal
- 4 Roentgenographic finding—skull may be abnormal

F MUSCULAR CRAMPS

- 1 Occurrence
 - a At rest
 - b During sleep
- 2 Characteristics
 - a Only one lower limb usually involved at a time
 - b Elderly people more frequently affected
- 3 Laboratory data—normal

G IDIOPATHIC CHVOSTEK'S SIGN^o

- 1 Neuromuscular hyperexcitability as shown by positive Chvostek's sign
- 2 No other abnormalities of any kind demonstrable
- 3 Incidence—found in about 5 per cent of routine medical patients

- (2) Exception after removal of parathyroid adenoma with high alkaline phosphatase may remain low

II PRIMARY HYPOPARATHYROIDISM WITHOUT MANIFEST OR LATENT TETANY

- 1 History is not very significant
- 2 Symptomatology
 - a None
 - b Failing vision
- 3 Physical status (see 37 VI)
 - a No abnormalities
 - b Cataracts
 - c Chvostek's and Trousseau's signs may be negative
- 4 Blood chemical analyses
 - a Calcium (serum) may be as low as 6 mg %
 - b Phosphorus (serum) may reach 5 mg %

C CHRONIC HYPOPARATHYROID TETANY

- 1 History
 - a Subtotal thyroidectomy — delayed tetany may be due to gradual loss of blood supply to parathyroids
 - b Operation for cataracts, especially in younger age group
- 2 Symptomatology—see 37 XII
- 3 Physical status
 - a Cataracts or evidence of previous iridectomy
 - b The following signs are positive (see 36 XIII)
 - (1) Chvostek, not pathognomonic
 - (2) Trousseau may not be characteristically elicited
 - (3) Erb
 - (4) Pool
 - (5) Schlesinger
 - (6) Lust
- 4 Laboratory data
 - a Sulkowitch test is negative if serum calcium is below 7 to 8.5 mg %
 - b Calcium (serum)
 - (1) Is rarely, if ever below 4.5 mg %
 - (2) May be only slightly decreased especially if serum phosphorus is high
 - c Phosphorus (serum)
 - (1) Is rarely below 4 mg %
 - (2) May reach 16 mg % or more (see Chart 81)

XIV DIFFERENTIAL DIAGNOSIS

A DISORDERS WITHOUT TETANY

The following are excluded as being the result of hypoparathyroidism when normal serum calcium and phosphorus values are present

- 1 Cataracts
- 2 Mental depression or psychoses
- 3 Diarrhea
- 4 Ectodermal defects
- 5 Vitamin deficiencies

B CONDITIONS WITH TETANY (latent or manifest)

- 1 Tetanus
 - a Characteristics
 - (1) Risus sardonicus
 - (2) Lockjaw
 - (3) Rigidity of muscles
 - (4) Opisthotonos
 - (5) Tonic convulsive seizures
 - (6) Deep reflexes are hyperactive
 - (7) Profuse sweating
 - (8) Sensorium is perfectly clear
 - (9) Exhaustion
 - b Laboratory data
 - (1) Sulkowitch test—normal
 - (2) Normal serum
 - (a) Calcium
 - (b) Phosphorus

2 Avitaminosis D

- a Occurrence
 - (1) Rickets
 - (2) Spasmophilia
 - (3) Osteomalacia
- b Characteristics
 - (1) Skin lesions
 - (2) Cataracts are absent
 - (3) Signs of tetany may be present
 - (4) Bone deformities as in rickets
- c Laboratory data
 - (1) Calcium (serum)
 - (a) Normal — normocalcemic hypophosphatemic type
 - (b) Decreased — hypocalcemic normophosphatemic type
 - (2) Phosphorus (serum) (see above)
 - (a) Normal
 - (b) Decreased
 - (3) Alkaline phosphatase (serum) — may be increased
- d Roentgenographic findings — osteomalacia (see Fig 259, p 635)

- b Maintenance—to be determined by checking serum calcium levels
- c Notes
 - (1) More efficient than vitamin D³
 - (2) Adequate calcium intake advisable
- 3 Vitamin D (less expensive)
 - a Oral—50 000 unit capsules from 2 a week to 4 a day doses up to 500 000 daily have been reported (see 103 \1)
 - b Maintenance—dependent on serum calcium
 - c Note—calcium should also be prescribed
- 4 Parathyroid hormone unnecessary
- 5 Amphogel
 - a Indication—rarely needed
 - b Dosage, oral—120 to 160 cc daily
 - c Result—phosphate absorption reduced
- 6 Ammonium chloride¹⁹
 - a Indications
 - (1) Helpful in mild cases along with the administration of calcium lactate
 - (2) Theoretical value in tetany of alkalosis
 - b Dosage oral—1 to 2 Gm t i d
- 7 Thyroid (desiccated USP)
 - a Indications
 - (1) If tetany follows subtotal thyroidectomy
 - (2) For thyroid deficiency
 - b Dosage oral—2 gr (maximum dose) daily if tolerated
- 8 Diet
 - a Low phosphate
 - (1) Intake of 0.3 to 0.5 Gm a day is optimal
 - (2) Theoretically advisable but it is tiring and usually discarded by patients
 - (3) Avoidance of milk is sufficient
 - (4) Phosphate absorption lowered (questionable)
 - b High acid ash intake decreases
 - (1) Blood alkalinity
 - (2) Irritability of
 - (a) Nerves
 - (b) Muscles
- 9 General
 - a Vitamins if evidence of their deficiency

- b Cataracts
 - (1) Do not develop if blood calcium kept normal
 - (2) Should be removed when indicated
- c Changes in medication should not be made oftener than at 2 to 3 week intervals unless
 - (1) Signs of tetany are present
 - (2) Reversion for calcium develops
 - (3) Nausea vomiting and/or headache occur
- d Sulkowitch test by patient for daily urinary excretion of calcium
 - (1) If test is negative or slightly positive dosage of A T 10 or vitamin D is adequate
 - (2) If test is strongly positive patient may be receiving too much of either medication
- e For a long range treatment determination of serum calcium and phosphorus is more reliable than the use of the Sulkowitch test chiefly because of a variable renal threshold for calcium in hypoparathyroidism⁶⁰

XVII PROGNOSIS

A GENERAL

- 1 Excellent with adequate treatment
 - a Cataracts do not
 - (1) Develop
 - (2) Progress
 - (3) Recede
 - b Trousseau's sign disappears
 - c Chvostek's sign may remain but usually is not found with adequate therapy
- 2 Occasionally hypoparathyroidism is difficult to control
- 3 Complications develop in
 - a Untreated patients
 - b Long standing cases (see 37 \V)

XVIII CAUSES OF DEATH

A NATURAL CAUSES MOST COMMON

B CEREBRAL

- 1 Edema
- 2 Hemorrhage—theoretically possible

C SPASM

- 1 Cardiac
- 2 Diaphragmatic
- 3 Laryngeal

D CONGESTIVE HEART FAILURE (rare)

(c) Notes

- [1] Avoid extravasation about vein for it causes sloughing
- [2] Prompt relief of symptoms, effects last about 1 to 2 hrs
- [3] Continuous intravenous drip unnecessary rarely indicated after removal of parathyroid adenoma (see 38 XVI C5)

- b Results—excessive intake of calcium lowers serum phosphate by
- (1) Increased fecal excretion
 - (2) Deposition in bone

3 Parathyroid hormone

a Dosage

- (1) Intramuscular or subcutaneous
 - (a) Initial—50 to 100 units (1 cc = 100 units)
 - (b) Maintenance—10 to 20 units daily until effect of A T 10 or vitamin D occurs
- (2) Intravenous—20 units or more

(3) Notes

- (a) Intravenous injection may give dramatic response but usually need not be used
- (b) Maximum effect in 8 to 24 hrs peak in 15 hrs
- (c) Serum calcium level should be watched

b Results

- (1) The following are increased
 - (a) Phosphate excretion (urinary)
 - (b) Calcium absorption
- (2) Ineffective sometimes (see 37 XVI C 5)

4 Dihydrotachysterol (A T 10)³⁶

a Dosage

- (1) Oral—2 to 5 cc/24 hrs (1 cc = 125 mg)
- (2) Notes
 - (a) Full effect evident in several weeks
 - (b) Calcium may also be given

b Results

- (1) Urinary phosphorus excreted in greater amounts than with vitamin D^{1 48 0 3 68}
- (2) Calcium and phosphorus absorption increased

5 Vitamin D (see 103 XI)^{10 60}

a Dosage

- (1) Oral—100 000 to 400,000 international units a day (20,000 to 40,000 international units/mg)
- (2) Notes
 - (a) Calcium may be given with it
 - (b) Full effect in several weeks
 - (c) Nontoxic usually (see 103 XI I for overdosage)^{3 30}

b Results

- (1) Similar to A T 10
- (2) The serum phosphorus drop is not entirely due to a rise in serum calcium from increased absorption, but partly by a direct action of vitamin D on phosphorus excretion
- (3) This effect apparently does not occur readily if medication is given intramuscularly³⁹

6 Miscellaneous

- a Tracheotomy or laryngeal intubation may be indicated for severe laryngeal spasm
- b Avoid large quantities of milk during acute tetany because of its high phosphorus content, especially following removal of parathyroid adenoma in patients with⁹
 - (1) Extensive bone changes
 - (2) Very high serum phosphatase

II CHRONIC HYPOPARATHYROID TETANY

1 Calcium preparations

- a Calcium lactate or gluconate—1 or 2 teaspoonfuls (20 to 60 Gm) 3 or 4 times a day
- b Calcium chloride—30 per cent solution is suitable 2 to 4 teaspoonfuls well diluted with hot water or palatable liquid 3 to 6 times daily or enteric coated capsules in corresponding amounts

c Notes

- (1) Calcium lactate is preferred because it is better tolerated
- (2) Sufficient to control mild tetany
- (3) Albright and Reifenstein warn against long continued calcium chloride therapy⁸

2 Dihydrotachysterol (A T 10)^{4 60}

- a Oral— $\frac{1}{2}$ to 2 cc daily or every other day (1 cc = 125 mg)

of head hair Irregular pupils from previous iridectomy, corneal injection Fundi showed early edema central and nasal portions of disks blurred and no hemorrhages Cheilosis and rhagades Thyroid normal Heart rhythm regular, no murmurs Flatness at both lung bases, indicating fluid Vital capacity 1 000 cc Circulation time 24 sec Chvostek's sign positive bilaterally knee and ankle jerks absent Tremor of lips and tongue Ataxia with finger to nose test Left biceps reflex greater than right Abdominals absent Romberg's sign positive

Laboratory data Urine—specific gravity 1 015 to 1 028, epithelial cells, albumin present sugar absent calcium 37 mg/24 hrs RBC 4 900 000 and 5 200 000 Hgb 14 5 Gm WBC 10 700 to 11 000 Differential polymorphonuclears 68%, lymphocytes 28% eosinophils 4% Hematocrit 47% Prothrombin time (during treatment) 72% of normal NPN 30 mg % Total protein 7 Gm %, albumin 4 Gm % globulin 3 Gm % Serum calcium 4 1 mg % Serum phosphorus 9 0 mg % Sodium chlorides 693 mg % Serum alkaline phosphatase 3 4 Bu Carbon dioxide combining power 34 volumes % PSP (intravenous) 31% in 1 hr (74% normal) Bromsulphthalein dye 10% retained Spinal fluid pressure 300 mm of water Sedimentation rate 38 mm/hr Electrocardiogram, see Fig 242

Roentgenographic findings Bones normal in texture and calcium content Chest—some cardiac enlargement pleural effusion (see Fig 244) IV pyelogram normal

Treatment Bilateral chest tap 1 300 cc and 1 100 cc (1 700 mg total protein) High vitamin diet Intravenous B complex daily Sodium citrate was given with apparent drop in serum calcium (A convulsive seizure occurred at this point consisting of a peculiar aura with flexion contracture of forearms and extension of fingers Loss of consciousness lasting about one minute this was not tetanic but cerebral in origin) AT 10—5 cc for 6 days then 10 cc for 6 days (serum calcium rose to 8 2 mg %) Vitamin D 100 000 units daily Calcium lactate 2 teaspoonfuls t i d

Progress Discharge from hospital—remarkable relief of all symptoms and signs Vital capacity 200 cc Weight 115 lbs

MONTHS

- 2 Marked improvement. No dyspnea or edema Frequency Drinks 3 to 4 quarts of liquids daily Weight 124 lbs Pulse rate 96 Chest film—lungs and heart normal Nails regrowing Skin only no rhagades Some infection of sclerae Reflexes absent Fundi normal Serum calcium 11 3 mg % Serum phosphorus 3 4 mg % Vitamin D 150 000 units daily Vitamin B complex capsules b i d Calcium—2 tea spoonfuls t i d
- 4 Serum calcium 9 3 mg % Serum phosphorus 3 3 mg % On same regimen, except 100 000 units of vitamin D daily To stop this medication, and continue with calcium and vitamin B
- 6 Chvostek's sign positive Serum calcium 7 2 mg % Serum phosphorus 3 2 mg % Spinal fluid calcium 4 5 mg % Restarted vitamin D 200 000/24 hrs Vitamin B stopped
- 8 Serum calcium 7 0 mg % Serum phosphorus 4 9 mg % Serum chlorides 586 mg % Urea clearance 74% of normal Vitamin D omitted for 2 weeks
- 20 No complaints Weight 157 lbs BP 102/78 Pulse 72 Vitamin D and calcium continued
- 39 Nails are normal now Still has some erythema on his face Chvostek's and Trousseau's signs are positive BP 110/80 Excellent health Serum calcium 8 mg % Serum phosphorus 2 8 mg % Sulkowitch test Grade 2 EKC normal Chest film—no change since last examination No calcium for 8 months To take 100 000 units of vitamin D daily again

Comment A case of primary idiopathic hypoparathyroidism causing cataracts for which an operation was necessary about 10 years ago Onset of tetanic manifestations 9 years or so later This disorder probably interferes with vitamin absorption from the gastro intestinal tract or their utilization is retarded The prompt reaction to vitamin B injections suggests that the latter thesis is unlikely

PRIMARY IDIOPATHIC HYPOPARATHYROIDISM WITH CATARACTS, BUT WITHOUT TETANY

PROTOCOL XXV

Family history Negative*Past medical* Only illness diphtheria at 17*Chief complaints* Diminished vision from bilateral cataracts for 18 months*History of present illness* Deafness in right ear which patient says is congenital for his grandfather and sons have it Some stiffness of joints*Physical examination* Age 59, male married, 3 children Weight 180 lbs Height 73 in with shoes Pulse 60 BP 110/80 Early arcus senilis and bilateral cataracts Slight colloid changes in thyroid Chvostek's and Trousseau's signs negative Vital capacity 3 600 cc

Laboratory data RBC 4,700,000 Hgb 96%
WBC 6,550 Differential polymorpho
nuclears 65%, lymphocytes 27%, mono
cytes 6 5%, eosinophils 1 5% Coagulation
time 6, 12, 12 15 min Firm clot re
traction Sugar 98 mg % 4 hrs after eat
ing NPN 35 mg % Uric acid 3 0 mg %
Total protein 7 09 Gm % Serum calcium
6 6 mg % Serum phosphorus 4 3 mg %,
4 hrs after eating BMR minus 9%

Röntgenographic findings Calcium content of bones normal*Treatment* Patient had cataracts removed 30 gr calcium and parathyroid hormone 1/10 gr were prescribed elsewhere*Progress and Treatment*

MONTHS	CALCIUM MG %	PHOSPHORUS MG %	THERAPY
5	6 5	5 3	Calcium lactate 6 heaping teaspoonfuls daily
6	7 0	4 7	As above
8	10 5	4 2	As above and viosterol 3 drops t.i.d
10	7 0	4 5	As above but viosterol stopped
17	9 2	4 4	As above
29	7 9	4 4	Medication taken irregularly

Comment An unusual case of hypocalcemia without a demonstrable cause and no manifest or latent tetany by the ordinary clinical tests The ease with which the serum cal

cium rose with calcium and viosterol and the elevated serum phosphorus favors the diagnosis of hypoparathyroidism

HYPOPARATHYROIDISM

PROTOCOL XXXI Figs 242, 244

Primary idiopathic hypoparathyroidism with secondary multiple vitamin deficiencies beriberi heart (?) with congestive failure, cataracts unilateral seizures (tetany)

Family history Negative*Past medical* Cataracts (bilateral) removed at age of 32 Patient denied any physical or mental symptoms prior to or since cataract operation until present illness Diet has been normal in all respects*Chief complaint* Spasm of extremities*History of present illness* Sudden fall with loss of consciousness and later stiffness of right arm Increasing shortness of breath orthopnea and edema of ankles Recurring spasms of left arm and leg beginning 9 months previously about once a week and increasing to once or twice daily Similar attacks began on right side 4 months previ

ously and continued 1 or 2 times a day having disappeared on left side Dilantin sodium diminished the number of attacks Fourteen days before admission forceful vomiting occurred after breakfast without any previous nausea He could eat and retain another meal after this Loss of energy and libido Mental depression but memory normal

Physical examination Age 44 male married Slightly cyanotic patient with a rather dull masklike expression sitting in bed and breathing with some difficulty Weight 136 lbs Pulse 90 BP 80/60 to 110/60 Seborrheic dermatitis Defective nails Patchy loss

- de origen paratiroideo simulando sindromes agudos quirurgicos J Internat Coll Surgeons 5 320 322 (July Aug) 1942
16. Cantarow A Stewart H L and Morgan H R Chronic idiopathic parathyroid tetany Endocrinology 24 556 564 (Apr) 1939
17. Cantor M M and Scott J W Chronic idiopathic hypoparathyroidism Canad M A J 47 551 552 (Dec.) 1942
18. Cope O Endocrine aspect of enlargements of parathyroid glands Surgery 16 273 288 (Aug) 1944
19. Curtis G M and Bertman M H Blood iodine studies blood iodine in nonthyroid disease Arch Surg 54 541 554 (May) 1947
20. Davidson J K Adolescent myxedema accompanied by nephrosis and by tetany of parathyroid origin treated with thyroid and Colp's parathyroid extract Canada M A J 15 803 805 (Aug) 1925
21. Drake T G Albright F Bauer W and Castleman H Chronic idiopathic hypoparathyroidism report of six cases with autopsy findings in one, Ann Int Med 12 1751 1765 (May) 1939
22. Eaton L M and Haimes S F Parathyroid insufficiency with symmetrical cerebral calcification J A M A 113 749 752 (Sept) 1939
23. Edmondson H A and Berne C J Calcium changes in acute pancreatic necrosis, Surg Gynec. & Obst 79 240-244 (Sept) 1944
24. Edmondson H A and Fields I A Relation of calcium and lipids to acute pancreatic necrosis report of 15 cases in one of which fat embolism occurred Arch Int Med 69 17 190 (Feb) 1942
25. Ellsworth R Diagnosis and treatment of parathyroid underfunction Internat Clin 3 27 45 (Sept.) 1933
26. Emerson K Jr and Beckman W W Calcium metabolism in nephrosis description of abnormality in calcium metabolism in children with nephrosis J Clin Investigation 24 564 572 (July) 1945
27. Emerson K Jr Walsh H B and Howard J E Idiopathic hypoparathyroidism a report of 2 cases Ann Int Med 14 1256 1270 (July) 1941
28. Evans J A and Elliott F D Multiple vitamin deficiencies including beriberi heart with congestive failure Lahey Clin Bull 4 1 3 181 (Oct) 1945
29. Fleischmann L Offizielles Protokoll der k. k. Gesellschaft der Aerzte in Wien Wien Klin Wchnschr 20 1455 (Nov.) 1907
30. Graybiel A and White P D Electrocardiography in Practice p 106 Philadelphia Saunders 1941
31. Greene J A and Swanson L W Psychosis in hypoparathyroidism Ann Int Med 14 1233 1236 (Jan) 1941
32. Hoesch K Parathyroid tetany Monatschr f Psychiat u Neurol (Suppl) 80 5 134 1937
33. — Die Epithelkörperchenepilepsie und die Epithelkörpercheninsuffizienz München med Wchnschr 84 467 469 1937
34. — Cataract and parathyroid epilepsy Deutsche med Wchnschr 63 1582 1585 (Oct) 1937
35. Hoffmann J Weiterer Beitrag zur Lehre von der Tetanie, Deutsche Zeitschr f Nervenheilk 9 2 8 280 1897
36. Holtz F Modern treatment of parathyroid insufficiency J Clin Endocrinol 1 453-458 (May) 1941
37. Howland J and Kramer H Factors concerned in the calcification of bone Tr Am Pediat Soc 34 84 208 1922
38. Hursthal L M Increased intracranial pressure associated with chronic parathyroid tetany Lahey Clin Bull 2 238 242 (Apr) 1942
39. — Unpublished data
40. Hursthal L M and Claibourne T S Treatment of tetany with dihydrotachysterol (AT 10) New England J Med 220 911 916 (June) 1939
41. Kellogg F. and Kerr W J Electrocardiographic changes in hyperparathyroidism Am Heart J 12 346 351 (Sept) 1936
42. Kendall E Jr, Walsh F B and Howard J E Idiopathic hypoparathyroidism a report of 2 cases Ann Int Med 14 1256 12 0 (Jan.) 1941
43. Lachman A Hypoparathyroidism in Denmark clinical study Acta med Scandinav suppl 121 1 269 1941
44. Learner N and Brown C L Ectodermal disorders in chronic hypoparathyroidism J Clin Endocrinol 3 261 264 (May) 1943
45. Leischer H Ueber epithelkörperchen Transplantation und deren praktische Bedeutung in der Chirurgie, Arch f klin Chir 84 208 222 1907
46. Leonard M F Chronic idiopathic hypoparathyroidism with superimposed Addison's disease in child J Clin Endocrinol 6 493 506 (July) 1946
47. Levy M S Power M H and Kepner E J Specificity of water test as diagnostic procedure in Addison's disease J Clin Endocrinol 6 607 632 (Sept) 1946
48. Liu S H A comparative study of the effects of various treatments on the calcium and phosphorus metabolism in tetany chronic adult idiopathic tetany J Clin Investigation 5 2 7 284 (Feb) 1928
49. — A comparative study of the effects of various treatments on the calcium and phosphorus metabolism in tetany chronic juvenile tetany J Clin Investigation 5 259 276 (Feb) 1928
50. Liu S H and Chu H I Studies of calcium and phosphorus metabolism with special reference to pathogenesis and effect of dihydrotachysterol (AT 10) and iron Medicine 22 103 163 (May) 1943
51. Marshall F A Tetany following mercurial diuresis J A M A 133 1007 1008 (Apr) 1947
52. McCarrison R The Thyroid Gland in Health and Disease New York Wood 1918 pp 151 165
53. McLean F C Activated sterols in treatment of parathyroid insufficiency review J A M A 117 609 619 (Aug) 1941
54. Mortell H J Idiopathic hypoparathyroidism with mental deterioration effect of treatment on intellectual function J Clin Endocrinol 6 266 274 (Mar) 1946
55. Odono J H Del Castillo E H Manfredi J F and De La Balze F A Parathyroid insufficiency and the human electroencephalogram J Clin Endocrinol 4 493-499 (Oct) 1944

TETANY ASSOCIATED WITH POLYCYSTIC KIDNEYS AND UREMIA ABSENCE OF PARATHYROID HYPLRPLASIA AND BONE CHANGE*

PROTOCOL XXVII

Past medical Accepted for insurance 3 years before admission

History of present illness One year previously, patient noted tingling on both sides of his face and fingers at time of an acute infection. This gradually disappeared four weeks before the first examination he had anorexia, progressive pallor, weakness and severe cramps in legs lasting 2 min or more.

Physical examination Age 30 years, male BP 130/70. Marked pallor. Fundi negative. Positive Chvostek's and Trousseau's signs. Kidneys not palpable.

Laboratory data Urine—albumin 2 plus specific gravity 1.010. Bence Jones negative. Sulkowitch negative. RBC 2,190,000. Hgb 59 Gm. WBC 8,500. NPN 175 mg %. Serum protein 8.2 Gm %. Serum calcium 4.4 mg %. Serum phosphorus 9.5 mg %. Carbon dioxide combining power 19 vol %. Serum chlorides 372 mEq %. Sedimentation rate 75 mm/hr. Subsequent serum total protein 6.3 Gm %, albumin 5.35 Gm %, and globulin 1.00 Gm %.

* We are indebted to the pathologic department of the Beth Israel Hospital, Boston, for the autopsy report.

Röntgenographic findings Skull negative. No change in bone structure or decalcification.

Treatment and course Patient transferred to Beth Israel Hospital for possible treatment with peritoneal lavage. His course was progressively downhill.

Postmortem examination Kidneys—small bilaterally polycystic, right larger than left and dilatation of one ureter presumably on congenital basis, chronic pyelonephritis. Parathyroids—only one identified, fat absent, chief cells exclusively present, size 0.5 x 0.3 cm. Interpretation—possibly prehyperplastic state but not hyperplasia on account of size and arrangement of cells. Remainder of postmortem examination essentially negative.

Comment The rapid termination and history indicate uremia of fairly short duration. The symptoms 1 year prior to admission suggest latent tetany. This may have been held in check by developing acidosis. If significant renal failure had been present long enough, parathyroid hyperplasia should have been found. Failure of hyperplasia may have been due to pre-existing hypoparathyroidism.

REFERENCES

- 1 Albright F. Metabolic effects of AT 10 (dihydroxycholesterol) compared with those of vitamin D and with those of parathyroid hormone. *Tr A Am Physicians* 53:221-226 (1938).
- 2 — The parathyroids—physiology and therapeutics. *JAMA* 117:527-533 (Aug) 1941.
- 3 Albright F, Bauer W, Cockhill J R and Ellsworth R. Studies on physiology of parathyroid glands: relation of serum calcium to serum phosphorus at different levels of parathyroid activity. *J Clin Investigation* 9:659-677 (Feb) 1931.
- 4 Albright F, Bloomberg E, Drake T and Sulkowitch H W. A comparison of the effects of AT 10 (dihydroxycholesterol) and vitamin D on calcium and phosphorus metabolism in hypoparathyroidism. *J Clin Investigation* 17:317-329 (May) 1938.
- 5 Albright F, Burnett C H, Smith P H and Paron W. Pseudo hypoparathyroidism—example of Seabright bantam syndrome: report of 3 cases. *Endocrinology* 30:922-932 (June) 1942.
- 6 Albright F and Reifenstein E C. The Parathyroid Glands and Metabolic Bone Disease. p 30. Baltimore: Williams & Wilkins 1948.
- 7 *Ibid* p 32.
- 8 *Ibid* p 39.
- 9 *Ibid* p 113.
- 10 Albright F and Sulkowitch H W. The effect of vitamin D on calcium and phosphorus metabolism: studies on four patients. *J Clin Investigation* 17:305-315 (May) 1938.
- 11 Bakwin H. Tetany in newborn infants. Relation to physiologic hypoparathyroidism. *J Pediatr* 14:1 (Jan) 1939.
- 12 Barr D P, MacBryde C M and Sanders T E. Tetany with increased intracranial pressure and papilledema: results from treatment with dihydroxycholesterol. *Tr A Am Physicians* 53:227-232 (1938).
- 13 Bell G O. Personal communication.
- 14 Blum H. Further use of dihydroxycholesterol (AT 10). *West J Surg* 49:113-119 (Feb) 1941.
- 15 Bu tos F M. Tetania de la pared abdominal



FIG 241 TROUSSEAU'S SIGN IN TETANY Elicited by from 3 to 5 minute application of sphygmomanometer cuff obliterating pulse (Swinton N W Postoperative parathyroid tetany New England J Med 217 165 169)

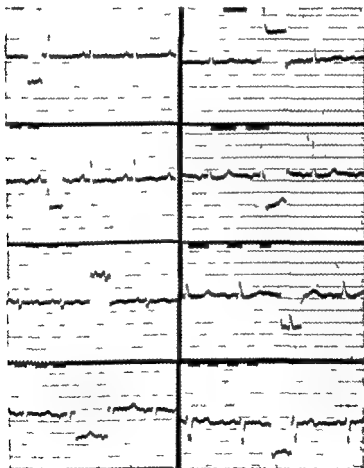


FIG 242 HYPOPARATHYROIDISM (See also Protocol 37 XVI and Fig 244) Electrocardiogram in idiopathic hypoparathyroidism Congestive heart failure was found Tracings (left) before therapy (right) after AT 10 and calcium was administered. Note the rise in T waves change in direction of P waves in leads II and III Part of these changes may be related to vitamin deficiency which was thought to be present The common change in hypoparathyroidism is lengthening of Q-T interval

- 56 Peters J W and Emerson L Influence of protein and inorganic phosphorus on serum calcium *J Biol Chem* 84 155 166 (Oct) 1929
- 57 Resch C A Dental findings in hypoparathyroidism in relation to patient and progeny, report of case *Cleveland Clin Quart* 14 147 152 (July) 1947
- 58 Rose E Hypoparathyroidism *Clinics* 1 1179 1196 (Feb) 1943
- 59 Sevringhaus H L Activated sterols and calcium salts in treatment of parathyroid tetany *Am J M Sc* 203 726 731 (May) 1942
- 60 Sevringhaus H L and St John H Parathyroid tetany treated with massive doses of vitamin D *J Clin Endocrinol* 3 635 637 (Dec) 1943
- 61 Siglin I S Eaton L M Camp J D and Haines S F Symmetrical cerebral calcification which followed postoperative parathyroid insufficiency report of case *J Clin Endocrinol* 7 433-437 (June) 1947
- 62 Soley M H Medical staff conference on parathyroid gland disease diagnostic features *Radiol* 39 719 720 (Dec) 1942
- 63 Sprague R G Haines S F and Powers M H Parathyroid *J Clin Endocrinol* 5 326 (Sept) 1945
- 64 Sutphin A Albright F and McCune D J Five cases (three in siblings) of idiopathic hypoparathyroidism associated with moniliasis, *J Clin Endocrinol* 3 625 634 (Dec) 1943
- 65 Swanton N W Postoperative parathyroid tetany *New England J Med* 217 165 169 (July) 1937
- 66 Taubenhaus M and Engle H M Clinical observations on case of idiopathic tetany and epilepsy *J Clin Endocrinol* 5 147 150 (Mar) 1945
- 67 Villaverde M Hypoparathyroidism with mental troubles and ectodermal disorders *J Clin Endocrinol* 8 584 585 (July) 1948
- 68 Weber F C and Richardson H H Parathyroid therapy dihydrotachysterol (A T 10) and mineral metabolism a metabolic study *J Clin Endocrinol* 1 32 37 (Jan) 1941
- 69 White P D and Mudd G Observations on effect of various factors on duration of electrical systole of heart as indicated by length of Q T interval of electrocardiogram *J Clin Investigation* 7 387 435 (Aug) 1929
- 70 Winer N J Hypoparathyroidism of probable encephalopathic origin *J Clin Endocrinol* 5 86 91 (Feb) 1945
- 71 Zondek H The Diseases of the Endocrine Glands, Baltimore Wood 1935 p 231
- 72 *Ibid* p 233



FIG 239 EVIDENT CHANGES IN NAIL BEDS IN IDIOPATHIC PRIMARY HYPOPARATHYROIDISM (See Fig 243) Grooved fingernails which appeared during initial period of treatment with dihydrotachysterol (A T 10) and calcium These eventually grew out



FIG 240 HYPOPARATHYROIDISM (See also Chart 82) Tetanic seizure in severe and untreated hypoparathyroidism (postoperative) This seizure was produced simply by rising from a sitting position

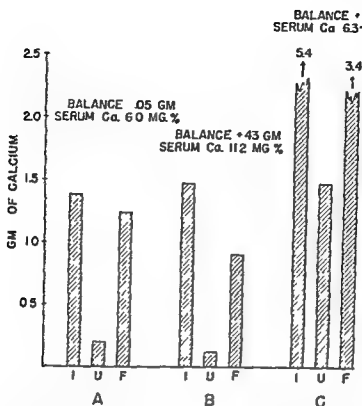


CHART 18 HYPOPARATHYROIDISM WITH TETANY
Effect of calcium and parathyroid extract on levels of serum urinary and fecal calcium (I = intake of calcium U = urinary excretion F = fecal excretion)

(A) Effect of 1.39 Gm of calcium (approximate daily requirement in normal) given orally to a case of untreated parathyroid tetany considered to have no functioning parathyroid tissue. Duration of experiment 5 days. Note that a normal relationship was not produced between urinary and fecal calcium indicating that calcium administered was not absorbed. There was no significant change in serum calcium (3 and 3.4 mg %) or in serum phosphorus (10.7 and 10.1 mg %). No clinical improvement. Calcium balance expressed in grams was slightly positive although equivocal.

(B) Effect of parathyroid extract on this case with approximately same calcium intake. Note that serum calcium rose to a normal value. Symptoms of tetany relieved. This chart shows that more calcium was absorbed in relation to intake than in (A) suggesting a local effect of parathyroid hormone on gastro-intestinal tract. Urinary output of calcium is still not in normal relationship to fecal calcium. Calcium must have been retained. Serum phosphorus not recorded here fell to 5.4 mg % due to greater urinary excretion of phosphorus.

(C) Result of high calcium intake some time after cessation of parathyroid extract. Serum calcium had not yet returned to original value (A). No symptoms of tetany had reappeared at this level of serum calcium. There was only a slight change in serum calcium and phosphorus concentrations with the high calcium intake although the urinary excretion of calcium was greater. This observation suggests that an increased intake of calcium produces greater gastro-intestinal absorption. However the previous effect of parathyroid hormone may have persisted (no tetany higher serum calcium) and thus influenced absorption. Both a high and low phosphorus intake was tried without significant changes in serum calcium and phosphorus levels. Urinary phosphorus excretion was increased with greater phosphorus intake. Since tetany did not reappear it may be accounted for by an improved calcium phosphorus ratio or possibly the satisfactory tissue content of calcium irrespective of the serum calcium level.

It is to be conjectured that large oral doses of calcium alone will not relieve tetany when no functioning parathyroid tissue exists. Parathyroid hormone may facilitate calcium absorption as well as the level of serum calcium (Albright F and Ellsworth P. Studies on the physiology of the parathyroids. Calcium and phosphorus studies on a case of idiopathic hypoparathyroidism. J Clin Investigation 7: 183-201).

FIG 243 IDIOPATHIC HYPOPARATHYROIDISM (See also Fig 239) Age 39 Bilateral calcification in ventricles Four year history of increasing fatigue loss of libido headaches tinnitus without deafness visual disturbance numbness in face and extremities unsteady gait slow speech and inability to concentrate Positive Chvostek's and Trousseau's sign Eye examination revealed changes consistent with hypoparathyroidism (Sulkowitch test negative) Serum protein 6.8 Gm % Serum albumin 4.7 Gm % Serum globulin 2.1 Gm % Serum calcium before treatment 5.1 and 6.2 mg % Serum phosphorus 4.4 and 5.1 mg % Serum alkaline phosphatase 2.6 B u Improvement marked on dehydrotachysterol and calcium Serum calcium 8.2 and 10.5 mg % Serum phosphorus 3.8 and 4.4 mg % on treatment The bizarre complaints lead frequently to a diagnosis of neurosis but the cerebral calcification raised the question of an intracranial lesion Oxygen encephalograms showed normal ventricular filling the calcification appeared to line the ventricular walls Calcification was noted in pelvic and leg arteries The finding of a low serum calcium and physical signs of tetany established the diagnosis after a 4 year illness

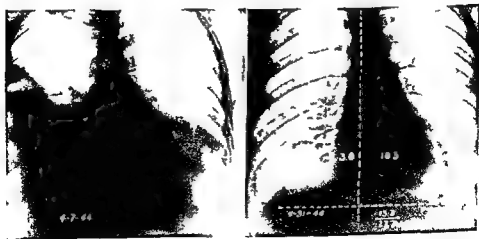


FIG 244 HYPOPARATHYROIDISM (See also Protocol 3, XVI and Fig 242) Heart in hypoparathyroidism before (left) and after (right) treatment Note fluid in chest and larger heart shadow on left Patient has remained well on vitamin D and calcium for 3 years

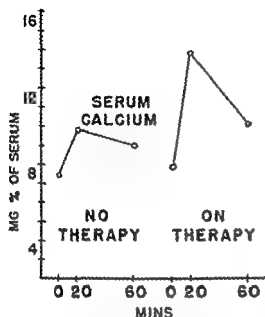


CHART 80 SERUM CALCIUM CURVES AFTER INTRAVENOUS INJECTION OF CALCIUM GLUCONATE (see Chart 79) (Left) Before vitamin D therapy (Right) While taking vitamin D and calcium orally

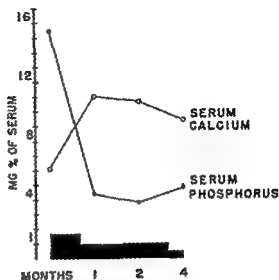


CHART 81 TETANY Postoperative hypoparathyroidism with tetany and unusually high phosphorus

Past medical Three operations for thyroid disease Unsuccessful therapy elsewhere with oral calcium until vitamin D administered

History Age 26 Frequent tetanic attacks and great lassitude Tetany worse following catamenia Parathyroid extract is said to have increased the exophthalmos

Laboratory findings NPN 24 mg % PSP 30% in 30 min The high serum phosphorus plotted in chart is average of 2 determinations (16.2 and 14.7 mg %)

Treatment Calcium lactate 3 heaping tea spoonfuls daily Vitamin D in doses of 150,000 units a day were given initially and finally reduced to 50,000 which as the chart shows was not adequate Vitamin D appears to have been as effective as dehydrotachysterol in mimicking the action of parathyroid hormone by producing an increased phosphorus excretion and a normal serum phosphorus

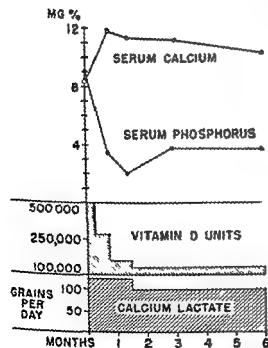


CHART 82 HYPOPARATHYROIDISM WITH TETANY (See also Fig 240) Vitamin D therapy in severe postoperative parathyroid tetany Note that serum calcium was only moderately depressed but that serum phosphorus was high Patient developed severe hypertension but renal function studies were normal The response to vitamin D and oral calcium gives evidence of adequate renal function for the serum phosphorus was decreased to 2 mg % There were no definite symptoms from hypercalcemia

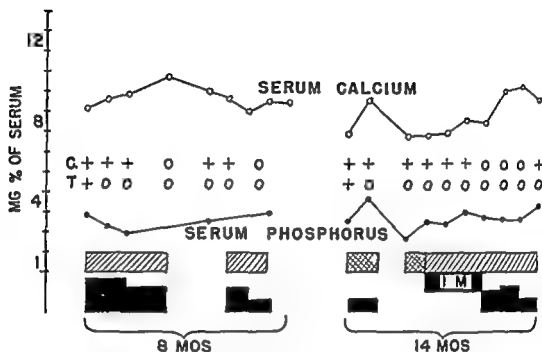


CHART 79 IDIOPATHIC HYPOPARATHYROIDISM Age 29 female Hypoparathyroidism with clinical tetany but with only slight change in serum calcium and phosphorus. Over a period of 9 years patient had intermittent stiffness of arms and facial muscles initiated by noise, confusion and emotion. Attacks lasted about an hour and she rarely had more than 2 to 3 spells each year. Thumbs adducted during attacks. Tingling of face and hands almost continuously. Eating habits normal. Positive Chvostek's and Trousseau's signs.

Serum calcium 9.1 mg % Serum phosphorus 4.0 mg %. All signs of tetany disappeared on treatment with vitamin D and calcium. Serum calcium rose to 10.9 mg %. When 20 cc of 10% calcium gluconate was injected intravenously (Chart 80) the rise in serum calcium was slight as compared with the rise when on therapy. Note decreasing level of serum calcium 3 years later without treatment. Failure to obtain relief with intramuscular vitamin D 400,000 units 2 to 3 times a week is noteworthy. Ammonium chloride and calcium without vitamin D did not control tetany.

This case illustrates that vitamin D and calcium therapy in tetany may be of value when the usual low calcium and high phosphorus are not found.

Solid block represents vitamin D orally beginning with 150,000 units daily. I M indicates intramuscular vitamin D (Deratol). C means Chvostek's sign. T stands for Trousseau's sign. Plus = present, zero = absent. Single cross-hatched block represents calcium lactate 3 large teaspoonfuls daily. Double cross-hatched area indicates ammonium chloride and calcium.

■ Moisture	Normal
d Eruptions	Normal
■ Pigmentation	Normal
f Color	Normal
2 Hair	
a. Head	Normal
b Facial	Normal
c Axillary	Normal
d Pubic	Normal
e Body	Normal
F HEAD	
1 Shape and size	Normal
2 Facial expression	Normal
3 Eyes	
a General	Normal slit lamp examination may reveal that conjunctivae of palpebral fissure area contain small glasslike particles ¹⁴³ presumably amorphous calcium deposits corneal changes consist of grayish granular epithelia and sub epithelial deposits running concentrically with limbus on either side or both, not pathognomonic of hyperparathyroidism for it is also found in other hypercalcemic conditions ⁶⁴ may be transient lesions in conjunctivae
b Fundi	Normal
c. Visual	
(1) Fields	Normal
(2) Activity	Normal
4 Ears and nose	Normal or may have calcium deposits in ear drums ⁴⁴ deafness may occur
5 Mouth and throat	
a General	Normal or fibrous tumor of gums (epulides) seeded on jaw ¹ red tongue
b Teeth	Malocclusion and disarrangement occasionally, may fall out ¹ & ¹²⁵
c Larynx (voice)	Normal
G NECK	
1 General	Parathyroid tumor may be palpated in 10 per cent ¹⁰⁴
2 Thyroid	Normal usually, may contain parathyroid adenoma
H CHEST	May show deformity due to bent ribs and spinal curvature
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal
2 Rate and rhythm	Normal
3 Blood pressure	Normal or elevated
4 Peripheral arteries and veins	May be sclerotic
5 Vasomotor	No data
J BREASTS	
1 Male	Normal
2 Female	Normal
K ABDOMEN	
1 Liver	Normal
2 Spleen	Normal
3 Hernia	None
4 Tumor	None

SECTION 38

PRIMARY HYPERPARATHYROIDISM

SYNONYMS

Acute hyperparathyroidism
Parathyroid poisoning²

Hyperhyperparathyroidism
Chronic hyperparathyroidism

NOTE The following are actually complications and not synonyms
Osteitis fibrosa generalisata
Osteitis fibrosa cystica or von Recklinghausen's disease

I DEFINITION

A condition due to excessive parathyroid secretion with an increase in urinary excretion of calcium and phosphorus which may lead to formation of renal calculi and/or generalized decalcification, fibrocystic lesions or tumors of the skeleton

II APPEARANCE

Normal, except when marked bony deformities, as kyphosis scoliosis, fractures and distortion of the limbs are present (see Fig 245)

III AGE

From 10 to 80^{33 43 104} (greatest incidence of parathyroid adenomas is around 45 years), also in infants¹¹³

IV SEX

Females more often affected than males, ratio 3 or 4 : 1 (adenomas)^{33 9 104}

V MENTAL DEVIATIONS

- | | |
|-----------------------|---------------------------------|
| A INTELLIGENCE | Normal |
| B RESPONSIVENESS | Normal |
| C OTHER ABNORMALITIES | May have delirium in acute type |

VI PHYSICAL STATUS

- | | |
|--------------------|---|
| A NUTRITION | Normal |
| 1 Weight | Decreased often |
| 2 Fat distribution | Not remarkable |
| B HEIGHT | May be decreased because of vertebral involvement (see 38 VIII D) |
| C EXTREMITIES | |
| 1 Upper | Normal unless bone deformities occur |
| a Hands | Normal |
| b Fingers | Normal clubbing has been reported ^{1 7} |
| c Span | May be increased because of shrinkage of stature |
| 2 Lower | Normal or may be bowed |
| a Feet | Normal |
| b Toes | Normal |
| D SPINE | Normal round back, kyphosis or scoliosis |
| E INTEGUMENT | |
| 1 General | Normal |
| a Texture | Normal |
| b Temperature | Normal |

C BLOOD CHEMICAL ANALYSES

1 Sugar	Normal
2 Nonprotein nitrogen	Increased, if sufficient renal impairment
3 Protein	May be elevated on account of hemoconcentration with low serum protein serum calcium may be normal
a Albumin	Normal
b Globulin	Normal
c A/G ratio	Normal
4 Uric acid	No data
5 Cholesterol	Normal
6 Sodium	Normal
7 Potassium	No data
8 Calcium	Above 10 to 16 or 17 mg %, rarely 20 mg %
9 Phosphorus	Decreased
10 Phosphatase (alkaline)	Normal or increased with bone involvement ⁸⁵
11 Chlorides	Normal or decreased
12 Iodine	Normal ⁸⁶
13 Creatine	No data
14 Magnesium	Increased during relapse

D FUNCTION TESTS

1 Tolerance	
a Glucose	No data
b Glucose insulin	No data
c Insulin	No data
2 Adrenal water test	Positive in 2 cases ⁸⁷
3 Salt deprivation	No data
4 Balance	
a Nitrogen	Normal, if adequate protein intake negative right after parathyroidectomy ³⁹

E MISCELLANEOUS TESTS

1 Basal metabolic rate	Normal variations
2 Circulation time	No data
3 Sedimentation rate	No data
4 Specific dynamic action of protein	No data
5 Gastric analysis	Hyperacidity or achlorhydria
6 Electrocardiogram	Q T interval may be shortened ^{88 89}
7 Fecal calcium	Varies with amount ingested in normals on low calcium diet fecal excretion is 75 per cent of total, in hyperparathyroid patients on a low calcium diet it is only 20 per cent of total on a high calcium diet (over 1 Gm) fecal excretions from 12 to 70 per cent of total (see Chart 83)

F URINARY HORMONE ASSAYS

1 FSH	No data probably normal
2 LH	
3 Estrogens	
4 Pregnanediol	
5 17 ketosteroids	
6 11 oxysteroids	
7 Aschheim Zondek	
8 TSH	

L GENITALIA

1 Male

- a Penis Normal
- b Testes Normal
- Prostate Normal

2 Female

- a External Normal
- b Internal Normal

M NEUROMUSCULAR

1 Muscles

Hypotonus and decreased response to galvanic stimulation⁴⁸

2 Gait

Normal, unless hampered by bone pain or deformities

3 Body movement

Normal

4 Tremor

None

5 Paresthesias

If there is encroachment on nerves by bone softening

6 Reflexes

Normal

N SPEECH

Normal

VII LABORATORY DATA

A URINE

1 General

May be excessive in quantity (up to 12 1/24 hrs) and milky in appearance, calcium phosphate casts, especially with little or no albumin calcium sand, varying degrees of renal impairment pyuria and hematuria from pyelitis and/or pyelonephritis¹⁰

2 Special analyses

- a Sugar None
- b Albumin None, Bence Jones protein may be found
- c Nitrogen May be increased
- d Creatine No data
- Creatinine No data
- f Sodium No data
- g Potassium No data
- h Calcium (see Chart 140) Increased (positive Sulkowitch test), 70 to 90 per cent of total calcium output occurs in urine (10 to 30% in normals) (see Chart 83) no excess in some cases when

(1) kidney function is poor

(2) Due to questionable avitaminosis D with normal renal function¹²³

(3) Serum calcium is normal during a remission¹⁴³

i Phosphorus

Marked renal impairment may decrease output otherwise follows calcium excretion

j Chloride

May be increased

k Iodine

No data

B HEMATOLOGY

1 Red blood cells

Normal or may be increased due to hemoconcentration

2 Hemoglobin

Normal or may be increased due to hemoconcentration, anemia reported⁹

3 White blood cells

Normal

4 Differential

Normal

5 Coagulation time

Prolonged²³

6 Clot

Friable

IX ETIOLOGY

A UNKNOWN

B PARATHYROID

- 1 Adenoma
- 2 Hyperplasia
- 3 Carcinoma (very rare)
- 4 Indirect stimulus as
 - a Pregnancy
 - b Inadequate calcium intake¹⁶

C PARATHYROTROPIC HORMONE OF PITUITARY

—Although existence of this hormone has not been established it may be a factor here if hypersecreted

X PATHOLOGY

A GROSS

1 Parathyroids

- a Adenoma^{17 34 44 53 55 81 104 105 111 116 118}

(1) Incidence—86 per cent of cases of hyperparathyroidism

(2) Appearance

(a) Grayish brown as seen through capsule

(b) Cut surface — yellowish brown with red areas like splenic tissue

(c) The following may be found

- [1] Calcium deposits
- [2] Connective tissue septae
- [3] Hemorrhage
- [4] Necrosis
- [5] Infarction (rare)

(3) Remaining parathyroids

- (a) Normal or hypoplastic
- (b) Hyperplasia of chief cells has been noted at postmortem after removal of parathyroid adenoma¹¹⁷

(4) Location

	PER CENT
(a) Normal	90
(b) Aberrant	10
[1] Medias	
tinum	63 (approx)
[2] Thyroid	30
[3] Esophagus	7

(5) Weight

- (a) Mean—7 Gm
- (b) Maximum—120 Gm

(6) Volume—4 to 5 cc

(7) Number

- (a) Single—usually
- (b) Multiple—rarely

(8) Shape

- (a) Lobulated often
- (b) Irregular

(9) Function—a few adenomas are not hypersecretory

b Primary hyperplasia^{11 44 45 50 57 116 117 118}

(1) Incidence—14 per cent of cases of hyperparathyroidism

(2) Appearance—deeper brown than adenomas

(3) All glands are involved, but not equally

(4) Size—4 cm x 3 cm x 3 cm

(5) Weight—up to 20 Gm each

(6) Volume—may reach 35 cc

(7) Shape—more irregular than adenoma

(8) Cysts and pseudopods—present

c Cancer^{17 23 43 53 98 106 123}

(1) Incidence

- (a) Very rare
- (b) Data in reported cases has sometimes been inconclusive

(2) Appearance

- (a) Cut surface—tannish gray to reddish brown
- (b) Nodules are attached to adjacent structures

(3) Location

- (a) Lower glands affected about five times as often
- (b) Aberrant tissue in
 - [1] Thyroid
 - [2] Thymus

(4) Size—may be 3 cm in diameter to masses measuring 11 cm x 11 cm x 4 cm

(5) Shape

- (a) Irregular nodules
- (b) Ovoid or round

(6) Number—single gland involved in 90 per cent

(7) Consistency like that of normal liver

(8) Metastases late to

- (a) Surrounding tissues
- (b) Lymph nodes
- (c) Lungs

L GENITALIA

1 Male

a Penis	Normal
b Testes	Normal
c Prostate	Normal

2 Female

a External	Normal
b Internal	Normal

M NEUROMUSCULAR

1 Muscles

Hypotonus and decreased response to galvanic stimulation⁴⁹

2 Gait

Normal, unless hampered by bone pain or deformities

3 Body movement

Normal

4 Tremor

None

5 Paresthesias

If there is encroachment on nerves by bone softening

6 Reflexes

Normal

N SPEECH

Normal

VII LABORATORY DATA

A URINE

1 General

May be excessive in quantity (up to 12 l/24 hrs) and milky in appearance calcium phosphate casts especially with little or no albumin, calcium sand varying degrees of renal impairment pyuria and hematuria from pyelitis and/or pyelonephritis¹⁰

2 Special analyses

a Sugar	None
b Albumin	None, Bence Jones protein may be found
c Nitrogen	May be increased
d Creatine	No data
e Creatinine	No data
f Sodium	No data
g Potassium	No data

h Calcium (see Chart 140) Increased (positive Sulkowitch test), 70 to 90 per cent of total calcium output occurs in urine (10 to 30% in normals) (see Chart 83) no excess in some cases when
(1) Kidney function is poor
(2) Due to questionable avitaminosis D with normal renal function¹²³
(3) Serum calcium is normal during a remission¹⁴

i Phosphorus

Marked renal impairment may decrease output, otherwise follows calcium excretion

j Chloride

May be increased

k Iodine

No data

B HEMATOLOGY

1 Red blood cells

Normal or may be increased due to hemoconcentration

2 Hemoglobin

Normal or may be increased due to hemoconcentration anemia reported⁹

3 White blood cells

Normal

4 Differential

Normal

5 Coagulation time

Prolonged¹²³

6 Clot

Friable

- (3) Single or multiple cystic spaces
 - (4) Finely reticulated areas
 - d Long bones
 - (1) Greatest regeneration and repair at diaphyses
 - (2) Epiphyses show
 - (a) No change
 - (b) Decalcification only
 - 3 Kidneys
 - a Nephrocalcinosis
 - (1) Deposition of calcium within tubules
 - (2) Secondary nonspecific changes of severe disease
 - b Renal calculi²⁰
 - (1) Without infection
 - (a) Composition
 - [1] Calcium phosphate usually
 - [2] Calcium oxalate possibly
 - (b) Ratio is 2 or more parts of calcium to 1 part of phosphorus
 - (2) With infection and alkaline urine
 - (a) Composition
 - [1] Calcium phosphate
 - [2] Calcium oxalate
 - [3] Magnesium ammonium phosphate
 - (b) Ratio less than 2 parts of calcium to 1 part of phosphate
 - c Arteries
 - (1) Monckeberg type arteriosclerosis in long standing cases¹
 - (2) Intimal calcification^{11a}
 - (3) Necrosis^{11b}
 - 4 Metastatic calcification of any tissue
- b Serum
 - (1) Calcium—elevated
 - (2) Phosphorus—decreased
 - c Greater absorption of (see Chart 83)
 - (1) Calcium
 - (2) Phosphorus (probably)
 - 2 Hypercalcemia produces
 - a Decreased nerve or neuromuscular excitability of striated and smooth muscles
 - (1) Muscular
 - (a) Hypotonia²
 - (b) Weakness
 - (2) Constipation
 - (3) Hearing impaired
 - (4) Electrocardiographic changes
 - b Calcium deposition in
 - (1) Conjunctivae
 - (2) Corneae
 - 3 Hypercalciuria and phosphaturia and loss of other substances may result in
 - a Polyuria
 - b Urinary calcium phosphate sand
 - c Calcium deposits in renal tubules
 - d Stones
 - e Osseous abnormalities (see below)
 - 4 Bone changes
 - a Calcium may be lost from the bones depending in part on
 - (1) Severity of disease (amount of hormonal secretion)
 - (2) Greater excretion than intake of calcium
 - (3) Unusual skeletal
 - (a) Stress
 - (b) Strain
 - b Tumors from collection of
 - (1) Osteoblasts
 - (2) Osteoclasts
 - (3) Marrow supporting tissue
 - c Cysts from
 - (1) Loss of calcium
 - (2) Fibrous replacement
 - d Anemia from
 - (1) Marrow changes if sufficiently severe
 - (2) Other causes
 - 5 Calculi formation is
 - a Due to an excess excretion of calcium which is precipitated in the renal pelvis
 - b Favored by
 - (1) Decreased fluid intake

XI PATHOLOGIC PHYSIOLOGY

A CHRONIC HYPERPARATHYROIDISM

- 1 Effects of excess parathyroid hormone
 - a Urinary excretion of the following is increased
 - (1) Water
 - (2) Nitrogen
 - (3) Calcium
 - (4) Phosphorus except with severe renal impairment
 - (5) Chloride
 - (6) Base

G BIOPSY

- 1 Endometrial
- 2 Testicular

H VAGINAL SMEAR

I SEMEN ANALYSIS

} No data, probably normal

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL (see Figs 246-248)

- 1 Cranial vault

Osteoporosis, milairy in type rarely osteofibroma or giant cell tumor without skeletal involvement¹⁷⁹

- 2 Sella turcica

Normal

- 3 Mandible

Ground glass appearance, cystlike cavities closely meshed trabeculae

- 4 Sinuses

Normal

- 5 Teeth

Loss of lamina dura,¹³³ diminished caries, epulides

- 6 Eyes

Corneal calcification may be seen⁶⁴

B EPIPHYSEAL STATUS (bone age)

May be retarded

C LONG BONES (femurs, radii and ulnae especially)^{25, 27}

Normal in 55 per cent, the remainder show (see Fig 254)

- 1 Diffuse decalcification
- 2 Fibrous arrangement of trabeculae
- 3 Cysts, may be solitary
- 4 Fractures, but pseudofractures are unusual¹²⁰
- 5 Thinning of cortex
- 6 Medullary cavities which appear to be expanded

D VERTEBRAE

Osteoporosis mottling, compression, causing round back or kyphosis, scoliosis, often squashed or wedge shape or codfish type herniation of nucleus (see Figs 251 and 252)

E BONE TEXTURE

As above cancellous outline preserved in areas unaffected by cysts, fractures, etc

F MISCELLANEOUS

- 1 Chest (see Fig 250)

- a Deformity of ribs with marked loss of calcium
- b Intrathoracic adenoma may be seen directly or by visualization of the esophagus²⁷

- 2 Calculi may be

- a Small
- b Large
- c Unilateral
- d Bilateral
- e Multiple
- f Solitary
- g Ringed usually (calcium phosphate)
- h Renal
- i Vesical

- 3 Nephrocalcinosis^{10, 15, 141}

- a Calcification of renal parenchyma about the pyramids (tubules)
- b Diffuse involvement

- 4 Blood vessels—calcification may be noted

- 5 Metastatic calcification—more suggestive of secondary hyperparathyroidism associated with primary renal disease

- 6 Pelvis—changes as in long bones frequent site for bone cysts (see Fig 253)

B LABORATORY DATA

1 Borderline cases with equivocal blood findings

a Comment

(1) Urinary calcium excretion in normals may be doubled by injection of parathyroid extract without appreciable change in serum calcium level

(2) Low serum protein may mask elevation of serum calcium

(3) Renal failure may prevent usual decrease in serum phosphorus

(4) Ellsworth Howard test—failure to obtain increase in urinary excretion of phosphorus by injection of parathyroid extract may indicate

(a) Maximum response to intrinsic parathyroid hypersecretion

(b) Hyperparathyroidism providing renal function is adequate

b Quantitative urine calcium determination on 24 or 48 hr amounts

(1) Low calcium diet 4 to 7 days

(2) Patient should be ambulatory

(3) Values over 200 mg/24 hrs indicate an excess calcium excretion only but is evidence in favor of hyperparathyroidism

c Repeated serum (fasting) chemical analyses are significant if

(1) Calcium—above 10.5 mg %

(2) Phosphorus—below 3 mg %

(3) Alkaline phosphatase

(a) Normal if hyperparathyroidism is *not* associated with bone disease

(b) Increased

2 Early or mild cases

a Excess calcium in urine as shown by Sulzowitch test after 4 to 7 days on low calcium diet (no milk eggs or egg products)

b Calcium (serum)

(1) Normal

(2) Elevated slightly

c Phosphorus (serum)—lowered

d Alkaline phosphatase

(1) Normal

(2) Increased

3 Late cases

a Calcium (serum)—elevated

b Phosphorus (serum)—low, unless disease complicated by renal failure

c Alkaline phosphatase (serum)—high if bone changes are present or taking place

4 Spontaneous remissions are possible in all^{1,4}

C ROENTGENOGRAPHIC FINDINGS

1 Normal in 55 per cent⁷

2 Generalized decalcification

3 Skull

a Smooth, ground glass

b Fuzzy appearance

4 Teeth—lamina dura may be

a Absent

b Disappearing

5 Kidneys—stones

6 Cystic lesions (see 38 \ A 2, B 2 \ I A 4)

7 Bone tumors (see 38 \ A 2, B 2 \ I A 4)

8 Fractures

9 Vertebral compression

D GENERAL

1 Adenoma may be demonstrated

a Palpable adenoma in 10 per cent

b Visualized intrathoracic adenoma (rare)

(1) Plain chest films

(2) Displacement of esophagus⁵

2 Bone deformities

XIV DIFFERENTIAL DIAGNOSIS

A OSTEOMALACIA (SECONDARY HYPERPARATHYROIDISM)²⁷

1 Definitions

a Osteomalacia is a condition in which calcium salts fail to be deposited in normal and new osteoid tissue due to abnormal ratios in the level of calcium salts and inorganic phosphorus

b Rickets is osteomalacia occurring before epiphyseal closure and is identified by active proliferation of cartilage and other changes at the epiphyseal junction

2 Etiologic classification

a Hypovitaminosis D or avitaminosis D due to inadequate intake

(d) Liver

(e) Kidneys

(9) Hormonal inactivity in 50 per cent

2 Bones^{3 78 9}

a Normal in some cases

b Cysts

(1) Single

(2) Multilocular

c Hemorrhages

(1) Recent

(2) Old

d Evidence of marked bone resorption

(1) Bend easily

(2) Cut readily with a knife

■ Skull

(1) Bone resorption = slight

(2) Thickening of tables

f Vertebrae may be collapsed

g Order of involvement

(1) Vertebrae

(2) Sacrum

(3) Pelvis

(4) Skull

(5) Jaw

(6) Flat bones of thorax

(7) Short tubular bones of

(a) Hands

(b) Feet

h Fractures and deformities are found

B Microscopic^{3 43 61 62 104 105 123}

1 Parathyroids

a Adenoma (see Figs 255 and 256)

(1) Parenchyma

(a) Follicular structures are present

(b) Irregular blocks of epithelial (chief) cells

(c) Cystic areas

(2) Cellular changes

(a) Polyhedral types with distinct cell walls

(b) Pleomorphism = present

(c) Few mitoses which are not indications of malignancy

(d) Water clear cell type is found occasionally

(e) Oxyphil cell is unusual

(3) Actual malignancy is rare

b Primary hyperplasia (or hypertrophy)^{11 117}

(1) Parenchyma

(a) Alveolar

(b) Pseudoglandular

(c) Compact

(d) Cystic with hemorrhage

(2) Fatty tissue = absent

(3) Cells resemble normal water helle type

(a) Cytoplasm absolutely water clear

(b) Large and distended to 60 times their normal size (diameter 10 to 40 microns, nuclei 6 to 7 microns)

c Secondary hyperplasia

(1) Cells

(a) Size—normal

(b) All are involved

(c) Higher glycogen content than in

[1] Hypertrophy

[2] Adenoma

(2) Fat tissue—scant

(3) Mitoses—absent

d Cancer^{33 43 61 62 104 123}

(1) Fibrous septa divide lobules in to irregular size and shape

(2) Stroma

(a) Delicate fibrillar reticulum

(b) Many capillary vessels

(c) Blood and lymph vessel invasion by tumor cells

(3) Parenchyma

(a) Closely packed cords or nests of cells

(b) Follicles containing colloid may be found

(4) Cellular changes

(a) All types found

(b) Larger than normal usually

(c) Mitotic figures are variable in number

(d) Nucleoli are found

2 Bones (see Fig 258)

a Trabeculae are devoured by osteoclasts

b Connective tissue proliferation

c Marrow may show

(1) Fibrosis

(2) Giant cell tumors

(a) Hyperactivity and accumulation of large multinucleated giant cells osteoclasts

(b) These are not malignant

- (3) Serum
 - (a) Calcium, phosphorus, phosphatase as listed above
 - (b) The following are normal
 - [1] Carbon dioxide combining power
 - [2] Chlorides
 - [3] Carotinoids
 - [4] Vitamin A
 - [5] Vitamin K
- (4) Fecal calcium relatively increased if intake is adequate
- (5) Bones
 - (a) Changes are dependent on duration and severity of the disease
 - (b) Usual findings of rickets in childhood
 - (c) Demineralization of bone without loss of cancellous structure
 - (d) Bending
 - (e) Looser's zones (see 38 XIV A 5 e)
 - (f) Excess production of osteoid tissue
 - (g) Lamina dura may be absent
 - (h) Expansion of rib cartilages
- b Osteomalacia or rickets—failure of vitamin D and calcium absorption due to steatorrhea (see Fig 259)
 - (1) General
 - (a) Marked weakness
 - (b) Emaciation
 - (c) Gastro intestinal findings
 - [1] Anacidity may be present
 - [2] Diarrhea may or may not occur
 - (d) Tetany may be present with
 - [1] Low serum calcium
 - [2] Normal serum phosphorus
 - (e) No renal stones
 - (2) Urine
 - (a) Titratable acidity—normal
 - (b) Calcium—decreased
 - (c) Ammonia—normal
 - (3) Serum
 - (a) Protein
 - [1] Normal
 - [2] Low
 - (b) Cholesterol (plasma)—low
 - (c) Calcium, phosphorus and potassium—low
 - (d) Alkaline phosphatase—increased
 - (e) Carbon dioxide combining power
 - [1] Normal
 - [2] Low
 - (f) Lipase and diastase levels—may be altered
 - (g) Carotenoids—decreased
 - (h) The following are decreased
 - [1] Vitamin A level
 - [2] Vitamin K (prothrombin time)
 - [3] Vitamin E as shown by therapeutic response
- (4) Feces
 - (a) Calcium and phosphorus content are increased (non absorption)
 - (b) Undigested meat fibers
 - (c) High fat content
- (5) Bones
 - (a) Normal
 - (b) Decalcification or Looser's zones
- c Osteomalacia due to renal disease^{1 5 12 37}
 - (1) Tubular insufficiency without gross glomerular insufficiency (renal acidosis)
 - (a) General
 - [1] Nephrolithiasis or nephrocalcinosis may be present^{2 36}
 - [2] Rickets and dwarfism in childhood
 - [3] Potassium deficiency syndrome if not present may be precipitated by ammonium chloride administration³⁰
 - (b) Theory of renal acidosis from tubular impairment and production of osteomalacia
 - [1] Initial disorder
 - [a] Defective tubular function (cause unknown)
 - [b] Impairment of ammonia formation in tubules

- (2) Low urinary citrate level^{1 2}
- (3) Urinary tract infections
- (4) Repeated episodes of dehydration during any acute infection

■ Retarded by

- (1) High fluid intake
- (2) Decreased absorption of
 - (a) Calcium
 - (b) Phosphorus
 - (c) Vitamin D
- (3) Low intake of
 - (a) Calcium
 - (b) Vitamin D

- 6 Anorexia vomiting and secondary weight loss may be due to
 - a Hypercalcemia per se
 - b Other physiologic changes possibly

B ACUTE HYPERPARATHYROIDISM—Great excess of hormone causes in the following order^{1 9 20 21 22 23 24 25}

- 1 Marked and increasing hypercalcemia (over 17 mg %)
- 2 Polyuria
- 3 Dehydration
- 4 Calcium phosphate precipitation in
 - a Kidneys
 - b Other tissues
- 5 Oliguria or anuria
- 6 Renal failure
- 7 Hemoconcentration
- 8 Hyperphosphaturia
- 9 Uremia
- 10 Death²²

XII SYMPTOMATOLOGY

A ACUTE HYPERPARATHYROIDISM

- 1 Restlessness
- 2 Tachycardia
- 3 Prostration
- 4 Coma
- 5 Dehydration
- 6 Acute renal failure
 - a Urinary suppression
 - b Vomiting
 - c Headache

B CHRONIC HYPERPARATHYROIDISM

- 1 General vague complaints
 - a Fatigue
 - b Weakness
 - c Stiffness or aching of muscles
 - d Headache

2 Gastro intestinal

- a Polydipsia
- b Mild abdominal discomfort
- c Duodenal ulcer distress^{116 117}
- d Dryness of throat
- e Anorexia, especial distaste for milk and eggs
- f Nausea
- g Vomiting¹
- h Weight loss
- i Constipation

3 Genito urinary

- a Polyuria
- b Renal colic
- c Dysuria
- d Nocturia
- e Enuresis
- f Hematuria
- g Pyuria

4 Bone changes

- a Peripheral pain
- b Backache, sudden onset usually
- c Fractures
 - (1) Spontaneous
 - (2) Traumatic
- d Shrinking of stature
 - (1) Scoliosis
 - (2) Kyphosis
 - (3) Compression of vertebrae
 - (4) Bowing of legs
- e Pigeon breast
- f Tumors of¹⁹
 - (1) Jaws
 - (2) Metacarpals
 - (3) Metatarsals
 - (4) Ends of long bones

XIII DIAGNOSIS

A COMMENT

- 1 Hyperparathyroidism will be diagnosed according to the imagination and vigil of the physician
- 2 It should be considered with the following (see 38 XII)
 - a Polydipsia
 - b Polyuria
 - c Renal stones
 - d Bone pain (including back)
 - e Spontaneous fractures
 - f Decreased height
 - g Unexplained
 - (1) Fatigue
 - (2) Vomiting
 - h Muscular hypotonia

- [c] Chlorides (may be low)
- [d] Carotenoids
- [e] Vitamin A
- [f] Vitamin K (prothrombin time)
- (c) Bones as 5 ■ above
- (3) Osteomalacia or rickets due to glomerular failure with or without tubular disease
 - (a) General
 - [1] Hyperplastic parathyroid glands, may be 30 times normal size rarely do not respond¹¹
 - [2] Disorder may be indistinguishable from late or treated hyperparathyroidism¹¹²
 - [3] Tetany possible
 - [4] Signs of uremia
 - (b) Causes
 - [1] Glomerular nephritis
 - [2] Pyelonephritis
 - [3] Congenital¹⁰⁴
 - [a] Hypoplasia
 - [b] Malformation
 - [c] Congenital dilatation of ureters
 - [4] Polycystic kidneys
 - (c) Urine
 - [1] Findings of chronic nephritis
 - [2] Calcium
 - [a] Normal
 - [b] Increased
 - [3] Phosphorus
 - [a] Normal
 - [b] Increased
 - [4] Potassium—increased
 - (d) Serum
 - [1] Nonprotein nitrogen (blood)—elevated
 - [2] Calcium—usually decreased
 - [3] Phosphorus—elevated
 - [4] Alkaline phosphatase—increased
 - [5] Carbon dioxide combining power—low
 - (e) Feces—no data
 - (f) Bones
 - [1] 'Renal' rickets in childhood
 - [2] Generalized demineralization due to increased bone destruction as opposed to lack of calcification of newly formed osteoid tissue
 - [3] Pseudocystic resorption occasionally
 - [4] Metastatic calcification sometimes
- d Osteomalacia from idiopathic calcinuria (rare) (see 38 XIII II 1)¹³
 - (1) Urine
 - (a) Calcium—excessive
 - (b) Other findings—normal (compare with renal tubular disease)
 - (2) Serum
 - (a) Calcium
 - [1] Normal
 - [2] Decreased
 - (b) Phosphorus
 - [1] Normal
 - [2] Decreased
 - (c) Alkaline phosphatase—increased
 - (d) Other findings—normal
 - (3) Kidneys—pyelonephritis often
- e Milkman's syndrome*^{11 99 100}
 - (1) Definition—a form of osteomalacia characterized by spontaneous pseudofractures (Looser's zones) without generalized skeletal decalcification
 - (2) Etiology as for any type of osteomalacia presented above, although apparently it most frequently occurs in
 - (a) Renal tubular insufficiency (see 38 XIV A 5 c)
 - (b) Steatorrhea
 - (3) Pseudofractures (as in osteomalacia with generalized decalcification)
 - (a) There may be
 - [1] Multiple
 - [2] Spontaneous

* Albright et al believe the name should be retained even though it is osteomalacia, because of its characteristic radiologic appearance

- (1) Rickets
 - (a) Fetal
 - (b) Infant
 - (c) Childhood, up to usual time of epiphyseal closure
- (2) Adult osteomalacia
- b Hypovitaminosis D or avitaminosis D (and other vitamins) due to failure of absorption
 - (1) Idiopathic steatorrhea
 - (a) Celiac disease (children)
 - (b) Nontropical sprue (adults)
 - (2) Chronic pancreatitis
- c Hypovitaminosis D or avitaminosis D due to lack of response to ordinary amounts of this vitamin, without steatorrhea or kidney disease
- d Renal diseases
 - (1) Glomerular damage with or without tubular disease
 - (a) Renal rickets (infantilism up to usual time of epiphyseal closure)
 - (b) Osteomalacia and chronic nephritis
 - (2) Tubular disease only
 - (a) Renal acidosis due to
 - [1] Failure of ammonia formation
 - [2] Inability to secrete acid urine (conservation of base)
 - (b) Abnormal production of organic acids (Fanconi's syndrome)
- 3 Chemical classification as regards parathyroid response to calcium deficiency and as manifested by serum calcium phosphorus and phosphatase^{2 108}
 - a Normal parathyroid response
 - (1) Calcium—normal
 - (2) Phosphorus—decreased
 - (3) Alkaline phosphatase
 - (a) Normal—early before skeletal weakness stimulates the osteoblasts
 - (b) Increased—later after osteoblastic stimulation
 - b Normal parathyroid response which is ineffective because of paucity of available calcium
 - (1) Calcium—low
 - (2) Phosphorus—low
 - (3) Alkaline phosphatase—increased
 - c Absent or inadequate parathyroid response from defective or absent parathyroid tissue or, conceivably a lack of end organ response to hormone
 - (1) Calcium—low
 - (2) Phosphorus
 - (a) Normal
 - (b) Decreased (as in 3 b above)
 - (c) Increased — if glomerular failure
- 4 Stages or degrees of osteomalacia based on normal parathyroid response (see 3 b above)
 - a Blood alterations without bone change
 - (1) Calcium—normal
 - (2) Phosphorus—low
 - (3) Alkaline phosphatase—normal
 - b Blood alterations with abnormal bone activity without roentgenographic evidence
 - (1) Calcium—normal
 - (2) Phosphorus—low
 - (3) Alkaline phosphatase—increased
 - c Blood alterations with bone changes, i.e., Looser's zones,^{93 111} but without generalized decalcification (Milkman's syndrome)
 - (1) Calcium—normal
 - (2) Phosphorus—low
 - (3) Alkaline phosphatase—increased
 - d Blood alterations with obvious and advanced osteomalacia (see 3 b above)
 - (1) Calcium—decreased
 - (2) Phosphorus—decreased
 - (3) Alkaline phosphatase—increased
- 5 Clinical differentiation
 - a Osteomalacia or rickets—due to inadequate intake or utilization of vitamin D and calcium (as seen in the Orient)
 - (1) Tetany may be present when
 - (a) Calcium is low
 - (b) Phosphorus is
 - [1] Normal
 - [2] Decreased
 - (2) Urine
 - (a) Titratable acidity—normal
 - (b) Calcium
 - [1] Absent
 - [2] Decreased
 - (c) Ammonia—normal

- b Serum
 - (1) Calcium—up to 18 or 20 mg %
 - (2) Phosphorus—low
- 3 Testosterone in treatment of carcinoma of breast
 - a Hypercalcemia symptoms usually absent
 - b Cause for effect is obscure
 - c Calcium (serum)—may reach 15 to 16 mg %
- 4 Estrogens—as for testosterone
- 5 Milk and alkali taken in excess over long periods of time⁴
 - a Conjunctivae
 - (1) Calcium deposits
 - (2) Band keratitis
 - b Renal function impaired
 - c Serum
 - (1) Calcium—increased
 - (2) Phosphorus
 - (a) Normal
 - (b) Increased
 - d Improvement on low calcium intake
- 6 Sudden bodily immobilization^{12 5 6 107}
 - a Occurrence
 - (1) Children or adolescents
 - (2) Paget's disease¹¹⁴
 - b Kidneys
 - (1) Calcinuria—excessive (1,300 mg /24 hrs)
 - (2) Temporary insufficiency
 - c Serum
 - (1) Calcium—increased about 15 mg %
 - (2) Phosphorus—normal
 - (3) Alkaline phosphatase—normal
 - d Bones show acute osteoporosis
- 7 Multiple myeloma (see below)
- 8 Malignant metastatic lesions (see below)
- 9 Boeck's sarcoid (see below)
- 10 Giant cell tumor may simulate epulis due to hyperparathyroidism
- 11 Miscellaneous causes
 - a Polycythemia vera
 - b Leukemia
 - c Pellagra
 - d Increased carbon dioxide content of blood
 - e Acute bone atrophy
 - f Advanced nephritis
- D RENAL CALCULI (idiopathic)
 - 1 Five to 15 per cent of idiopathic renal calculi are proven eventually to have hyperparathyroidism^{1 34 37}
 - 2 Excess excretion of calcium without kidney disease except possibly in pyelonephritis¹¹
 - 3 Serum
 - a Calcium
 - (1) Normal
 - (2) Decreased (slightly)
 - b Phosphorus—normal
 - E CALCINOSIS
 - 1 Definition—abnormal deposit of calcium of unknown etiology in tissues⁸⁸
 - 2 Calcinosis universalis (see Fig 260)
 - a Palpable nodules of amorphous calcium involving
 - (1) Muscles
 - (2) Subcutaneous tissue
 - b Necrosis with draining sinuses may occur
 - 3 Dermatomyositis
 - a Tight skin similar to scleroderma
 - b Subcutaneous diffuse amorphous calcium deposits
 - 4 Metastatic calcinosis
 - a Hyperparathyroidism
 - b Hypervitaminosis D (see Protocol 38 XXVIII)
 - c Renal disease with secondary hyperparathyroidism
 - d Hypoparathyroidism
 - e Paget's disease
 - F BONE DISEASES
 - 1 Multiple myeloma (rarely confused with hyperparathyroidism)
 - a Definition
 - (1) A primary malignant tumor of bone marrow characterized by areas of hyperplasia of plasma cells affecting the flat bones
 - (2) The disease is rapidly fatal although numerous exceptions occur in which the process is prolonged or apparently healed
 - b Urine
 - (1) Casts
 - (a) Calcium
 - (b) Phosphate
 - (2) Bence Jones protein in 50 to 70 per cent of cases^{3 11 17}
 - (3) Calcium may be increased
 - c Serum
 - (1) Protein—increased to 12 Gm %⁸

- [c] Inability to secrete acid urine (i.e., to conserve base) which results in lowering of carbon dioxide and elevation of chlorides
- [d] Calcium is a sparer of base for acid excretion and excessive in urine
- [2] Results
 - [a] A low serum calcium stimulates parathyroid function
 - [b] Parathyroid hyperplasia in turn increases serum calcium to normal by causing hyperphosphaturia (excretion through glomeruli), hypophosphatemia and osteoblastic stimulation eventually
 - [c] If gastric acidity is low, absorption of calcium and phosphorus is decreased and may contribute to calcium deficiency^a
- (c) Kidneys
 - [1] Urine concentration (specific gravity)
 - [a] Normal
 - [b] Faulty
 - [2] Inulin clearance test—decreased
 - [3] Pyelonephritis may be present
- (d) Urine
 - [1] Titratable acidity—low
 - [2] Sugar—occasionally
 - [3] Calcium—increased
 - [4] Ammonia—low
 - [5] Organic acids—normal
- (e) Serum (see above)
 - [1] Sugar (blood)—may be low
 - [2] Potassium
 - [a] Normal
 - [b] Low
 - [3] Calcium—normal (rarely low)
 - [4] Phosphorus—low
 - [5] Alkaline phosphatase—elevated (usually)
 - [6] Chlorides—elevated
 - [7] Carbon dioxide combining power—low
 - [8] Carotenoids—normal
 - [9] Vitamin A level—normal
 - [10] Vitamin K (prothrombin time)—normal
- (f) Fecal calcium content may be as low as 20 per cent of urinary calcium
- (g) Bones
 - [1] Normal
 - [2] Decalcification and/or Looser's zones
- (2) Osteomalacia and rickets due to Fanconi's syndrome (derangement of amino acid metabolism with hyperaminoaciduria)⁹⁰
 - (a) Urine—increased excretion of
 - [1] Titratable acidity
 - [2] Cellular contents
 - [3] Sugar
 - [4] Calcium
 - [5] Phosphorus
 - [6] Ammonia
 - [7] Acetone
 - [8] Amino acids
 - [9] Cystine (at times)
 - (b) Serum
 - [1] Calcium
 - [a] Normal
 - [b] Low
 - [2] Phosphorus—low
 - [3] Alkaline phosphatase—high
 - [4] Carbon dioxide combining power—low
 - [5] The following are normal
 - [a] Sugar (may be decreased)
 - [b] Nonprotein nitrogen (blood)

- b Serum
 - (1) Calcium—up to 18 or 20 mg %
 - (2) Phosphorus—low
 - 3 Testosterone in treatment of carcinoma of breast
 - a Hypercalcemia symptoms usually absent
 - b Cause for effect is obscure
 - c Calcium (serum)—may reach 15 to 16 mg %
 - 4 Estrogens—as for testosterone
 - 5 Milk and alkali taken in excess over long periods of time⁴
 - a Conjunctivae
 - (1) Calcium deposits
 - (2) Band keratitis
 - b Renal function impaired
 - c Serum
 - (1) Calcium—increased
 - (2) Phosphorus
 - (a) Normal
 - (b) Increased
 - d Improvement on low calcium intake
 - 6 Sudden bodily immobilization^{12 75 6 107}
 - a Occurrence
 - (1) Children or adolescents
 - (2) Paget's disease^{11a}
 - b Kidneys
 - (1) Calcinuria—excessive (1,300 mg /24 hrs)
 - (2) Temporary insufficiency
 - c Serum
 - (1) Calcium—increased about 15 mg %
 - (2) Phosphorus—normal
 - (3) Alkaline phosphatase—normal
 - d Bones show acute osteoporosis
 - 7 Multiple myeloma (see below)
 - 8 Malignant metastatic lesions (see below)
 - 9 Boeck's sarcoid (see below)
 - 10 Giant-cell tumor may simulate epulis due to hyperparathyroidism
 - 11 Miscellaneous causes
 - a Polycythemia vera
 - b Leukemia
 - c Pellagra
 - d Increased carbon dioxide content of blood
 - e Acute bone atrophy
 - f Advanced nephritis
- D RENAL CALCULI (idiopathic)
- I Five to 15 per cent of idiopathic renal calculi are proven eventually to have hyperparathyroidism^{1 4 67}
 - 2 Excess excretion of calcium without kidney disease except possibly in pyelonephritis¹¹
 - 3 Serum
 - a Calcium
 - (1) Normal
 - (2) Decreased (slightly)
 - b Phosphorus—normal
- E CALCINOSIS
- 1 Definition—abnormal deposit of calcium of unknown etiology in tissues^{5a}
 - 2 Calcinosis universalis (see Fig 260)
 - a Palpable nodules of amorphous calcium involving
 - (1) Muscles
 - (2) Subcutaneous tissue
 - b Necrosis with draining sinuses may occur
 - 3 Dermatomyositis
 - a Tight skin similar to scleroderma
 - b Subcutaneous diffuse amorphous calcium deposits
 - 4 Metastatic calcinosis
 - a Hyperparathyroidism
 - b Hypervitaminosis D (see Protocol 38 XXVIII)
 - c Renal disease with secondary hyperparathyroidism
 - d Hypoparathyroidism
 - e Paget's disease
- F BONE DISEASES
- 1 Multiple myeloma (rarely confused with hyperparathyroidism)
 - a Definition
 - (1) A primary malignant tumor of bone marrow characterized by areas of hyperplasia of plasma cells affecting the flat bones
 - (2) The disease is rapidly fatal although numerous exceptions occur in which the process is prolonged or apparently healed
 - b Urine
 - (1) Casts
 - (a) Calcium
 - (b) Phosphate
 - (2) Bence Jones protein in 50 to 70 per cent of cases^{1- 71 77}
 - (3) Calcium may be increased
 - c Serum
 - (1) Protein—increased to 12 Gm %³

- [3] Uncalcified
- [4] Symmetrical, if not then they may be due to
 - [a] Trauma
 - [b] Other bone diseases, usually at site of bone pathology

(b) Location

- [1] Scapulae
- [2] Glenoid cavities
- [3] Ribs
- [4] Necks of femur
- [5] Pelvis

II CONDITIONS ASSOCIATED WITH DECREASED OR FAULTY FORMATION OF OSTEOID TISSUE

1 Osteoporosis^{8 117}

- a Definition—a disorder of tissue metabolism including decreased or faulty formation of osteoid tissue hence decreased total calcification

b Etiology

- (1) It may be associated with
 - (a) Acromegaly
 - (b) Cushing's syndrome
 - (c) Hyperthyroidism
 - (d) Eunuchoidism
 - (e) Menopause²²
 - (f) Diabetes mellitus (long standing and uncontrolled)

- (2) Malnutrition
- (3) Vitamin C deficiency
- (4) Disuse
- (5) Idiopathic

c Serum

- (1) Protein
 - (a) Normal
 - (b) Low
- (2) Calcium—normal
- (3) Phosphorus
 - (a) Normal
 - (b) Increased slightly⁷⁰
- (4) Alkaline phosphatase—normal

d Bones

- (1) Normal in most cases except for calcium content
- (2) Cortex becomes thin eventually
- (3) Osteoid tissue decreases
- (4) Rare cases reported with osteitis fibrosa^{124 130}
- (5) Skull—normal usually
 - (a) Dental caries (in eunuchs)
 - (b) Lamina dura persists

2 Osteogenesis imperfecta

a Hereditocongenital disease

b Serum

- (1) Calcium—normal
- (2) Phosphorus—normal
- (3) Alkaline phosphatase—normal (unless associated with avitaminosis D)

c Bones

- (1) Osteoporosis
- (2) Brittle
- (3) Thin cortex
- (4) Fractures are frequent
- (5) Deformities, such as bowing of legs
- (6) Lack phosphatase⁷⁴
- (7) Skull
 - (a) Deformed
 - (b) Failure of closure of sutures
 - (c) Otosclerosis
- (8) Cartilage—normal

d General

- (1) Short stature
- (2) Scleras
 - (a) White
 - (b) Blue
- (3) Poor dentition

C HYPERCALCEMIA

1 Hypervitaminosis D (see 103 VI for section on Vitamin D Fig 261)

- a Etiology—excessive dosage of vitamin D or A T 10 associated with normal or increased serum calcium, especially with renal impairment

b Symptoms same as for hypercalcemia (see 38 VII)

c Urine—increased output of

- (1) Calcium
- (2) Phosphorus (greater than calcium)

d Serum

- (1) Calcium
 - (a) Normal
 - (b) Increased
- (2) Phosphorus—increased
- (3) Alkaline phosphatase—increased

e Kidneys

- (1) Nephrocalcinosis
- (2) Renal insufficiency

f Metastatic calcification

- ### 2 Parathyroid extract given in excess
- a All symptoms associated with hypercalcemia

- (2) Multiple cutaneous fibromas are absent
 - d Serum
 - (1) Cholesterol (plasma)—normal
 - (2) Calcium—normal
 - (3) Phosphorus
 - (a) Normal
 - (b) Low
 - (4) Alkaline phosphatase—may be increased with extensive involvement¹⁸
 - e Bones
 - (1) Lesions regional in character
 - (2) Unilateral preponderance
 - (3) Unaffected areas are normal
 - (4) Sudden immobilization may cause same changes in serum calcium as in Paget's disease (see 38 XIV F 3)¹²⁴
 - (5) Pathologic fractures
 - (6) Lamina dura present
 - (7) Epiphyses and diaphyses may be affected
 - 5 Neurofibromatosis (von Recklinghausen's disease—see Fig 265)^{7 139}
 - a Onset—early in life
 - b Hypothalamic involvement
 - c Glioma of optic chiasm
 - d Skin⁷
 - (1) Multiple cutaneous neurofibromatosis (often familial)
 - (2) Areas of pigmentation with smooth edges
 - e Sexual precocity—rare in males
 - f Serum—the following are normal
 - (1) Cholesterol (plasma)
 - (2) Calcium
 - (3) Phosphorus
 - (4) Alkaline phosphatase
 - g Bones
 - (1) Lesions more symmetrical
 - (2) Tendency to involvement of
 - (a) Upper ends of tibiae
 - (b) Lower ends of femurs
 - (3) Less extensive damage than in polyostotic fibrous dysplasia
 - 6 Boeck's sarcoid²³
 - a Serum
 - (1) Protein—may be high
 - (2) Calcium—may be high
 - (3) Phosphorus—normal
 - (4) Alkaline phosphatase—may be high
 - b Bones
 - (1) Generalized decalcification absent
 - (2) Lamina dura present
 - (3) Small cystlike areas generally in
 - (a) Hands
 - (b) Feet
 - c Renal stones may be found
 - d Lung lesions are fairly typical
 - 7 Eosinophilic granuloma
 - a Serum—the following are normal
 - (1) Protein
 - (2) Calcium
 - (3) Phosphorus
 - (4) Alkaline phosphatase
 - b Bones
 - (1) Punched out areas of destruction occur in any part of the skeleton
 - (2) Lesions are radiosensitive
 - c Good prognosis
 - 8 Osteosclerosis fragilis generalisata¹⁴⁰
 - a Synonyms
 - (1) Osteopetrosis
 - (2) Marble bones
 - (3) Albers-Schonberg disease
 - (4) Osteitis condensans generalisata
 - (5) Osteopoikilosis
 - b Disease does not resemble hyperparathyroidism
 - c Parathyroids may be enlarged occasionally⁴
 - d Alkaline phosphatase (serum)—slightly elevated
 - e Bones
 - (1) Extensive osteoid calcification
 - (2) Metastatic calcification
 - (3) Normal lamellar structure is absent
 - 9 Other bone diseases should be considered but are unlikely to be mistaken for parathyroid disease if adequate studies are made
 - a Tuberculosis
 - b Syphilis
 - c Tumors
 - d Cysts
- G LIPOID DISEASES**
- 1 Gaucher's disease¹³⁷
 - a Familial tendency²
 - b Occurrence
 - (1) Youth usually
 - (2) Adults occasionally

- (2) Calcium
 - (a) Normal
 - (b) Increased (18-20 mg %)
 - 40-120
- (3) Phosphorus—may be low, if renal function adequate
- (4) Alkaline phosphatase^{110 140}
 - (a) Normal
 - (b) Increased slightly
- d Renal
 - (1) Nephrocalcinosis¹¹⁰
 - (2) Calculi
 - (3) Insufficiency
- Bones (see Fig 262)
 - (1) Generalized demineralization occasionally
 - (2) Punched out areas (see 38 XIV F 7)
- f Plasma cells in blood smear and sternal puncture reveals diagnosis
- 2 Malignant metastatic disease in bone³⁸
 - a Organs from which metastatic lesions frequently occur
 - (1) Thyroid
 - (2) Breasts
 - (3) Bronchi
 - (4) Kidneys
 - (5) Prostate (acid serum phosphatase elevated)
 - b Sites of metastases (usually well vascularized locations)
 - (1) Skull
 - (2) Ribs
 - (3) Sternum
 - (4) Vertebrae
 - (5) Proximal ends of
 - (a) Humeri
 - (b) Femurs
 - c Destructive lesions are common with or without general demineralization
 - d Bone biopsy ■ diagnostic
 - e Blood chemical analyses
 - (1) Normal
 - (2) Simulate primary hyperparathyroidism in all respects
 - f Primary tumor may be located
- 3 Osteitis deformans (Paget's disease)
 - a Definition—a bone disease of unknown etiology characterized in advanced cases by various deformities as
 - (1) Bowing of legs
 - (2) Skull enlargement
 - b Disease occurs at all ages
 - c Process may be asymptomatic
 - d Urine
 - (1) Calculi may form
 - (2) Calcium is not increased, except in sudden bodily immobilization because of fracture (see 99 V, 103 X)¹¹⁴
 - (a) When osteoblastic activity is temporarily reduced
 - (b) Excess osteoclastic activity (always present) continues
 - e Serum
 - (1) Calcium
 - (a) Normal
 - (b) Increased
 - (2) Phosphorus—normal
 - (3) Alkaline phosphatase—to 150 Bu or more
 - f Bones
 - (1) Osteoblastic and osteoclastic activity are increased
 - (2) Size increased
 - (3) Trabeculations are coarse
 - (4) Skull (see Fig 263)
 - (a) Thick
 - (b) Moth eaten
 - (c) Lamina dura present
 - (5) Biopsy shows a mosaic appearance of cement lines (junction between new and old bone) within trabeculae which ■ pathognomonic⁶⁸
 - g Diagnosis is usually made by roentgenograms
- 4 Polyostotic fibrous dysplasia^{7 14 18, 62, 63 68 69 90 ■ 101}
 - a Synonyms
 - (1) Osteodystrophia fibrosa unilateralis
 - (2) Fibrous osteodystrophy
 - (3) Unilateral von Recklinghausen's disease
 - (4) Fibrous dysplasia
 - (5) Osteitis fibrosa disseminata
 - b It has been found in
 - (1) Gigantism
 - (2) Hyperthyroidism (rare)
 - (3) Sexual precocity in females (Albright's disease)^{10 67}
 - (4) Diabetes mellitus¹⁰⁹
 - c Skin
 - (1) Pigmented areas, irregular edges

- 3 Myxedema⁸⁴
- 4 Paget's disease
- 5 Duodenal ulcer^{116 117}
- 6 Aritamiasis D

XVI TREATMENT

A MEDICAL

- 1 Indications—high serum calcium level (17 mg % or over) to lessen impending danger of²³
 - a Renal failure
 - b Excessive hypercalcemia before surgery
- 2 Therapy
 - a High fluid intake, including intra venous saline
 - b Low calcium (below 0.25 Gm a day) and phosphorus diet
- 3 Results—management should be helpful temporarily

B ROENTGEN

- 1 Indications—if
 - a Surgery is
 - (1) Refused
 - (2) Contraindicated
 - b At operation
 - (1) Part of adenoma is not removed
 - (2) Tumor is not found
- 2 Results
 - a Isolated cases may respond favorably
 - b Generally disappointing⁷

C SURGICAL (see Figs 266 and 267)

- 1 Indications—to
 - a Prevent kidney damage
 - b Avoid further bone involvement
 - c Relieve symptoms
- 2 Comment
 - a Adequate knowledge of parathyroid embryology is helpful¹⁰⁴
 - b Special skill is required in this field^{56 87 95}
 - c Size of adenoma or parathyroid hypertrophy may roughly parallel severity of disease
 - (1) If small adenoma (1 to 2 cm) is found in an advanced case a larger one must be sought
 - (2) All adenomas should be removed (see 34 \)
 - (3) Finding of one normal gland
 - (a) Hypertrophy of the other parathyroids excluded

(b) Adenoma is therefore present, if the diagnosis is correct

(4) Subtotal resection of all hypertrophic glands is necessary (see 38 \)

(5) Normal glands should not be removed

d High serum phosphatase is considered an indication, by some for removal of parathyroid pathology in stages to avert severe postoperative tetany (see 38 \VI C 5)⁷⁷

e With renal damage, less radical resection is required because parathyroid secretion is necessary to compensate for

- (1) Rise in serum phosphate
- (2) Depression of serum calcium

f Removal of carcinoma follows the surgical principles for any malignant process

3 Operation for parathyroid adenoma

- a Anesthesia
 - (1) General
 - (2) Nitrous oxide ether
 - (3) Cyclopropane
- b Exploration of neck^{1 103}
 - (1) Wide collar incision
 - (2) Platysma elevated with skin flaps
 - (3) Sternomastoid dissected free of sternothyroid and omohyoid opposite cricoid cartilage sufficiently to see ansa hypoglossal nerve
 - (4) Sternothyroid muscles divided in midline from thyroid cartilage to manubrium
 - (5) Prethyroid muscles are cut transversely
 - (6) Contour of thyroid inspected for tumor mass
 - (7) If none is found lobe is freed with complete lateral exposure
 - (8) Inferior thyroid artery and recurrent nerve are located
 - (9) Inspect for superior glands from inferior thyroid artery to upper pole and above
 - (10) Parathyroids may lie on lateral anteroposterior or medial surface of thyroid

- e Physical status
 - (1) Patchy pigmentation of skin
 - (2) Fever
 - (3) Splenomegaly
 - (4) Hepatomegaly
 - d Blood count
 - (1) Normocytic normochromic anemia
 - (2) Leukopenia, relative lymphocytosis
 - (3) Thrombopenia with hemorrhagic tendency
 - e Serum chemical analyses
 - (1) The following are normal
 - (a) Cholesterol (plasma may be decreased)
 - (b) Calcium
 - (c) Phosphorus
 - (d) Alkaline phosphatase
 - (2) Bilirubin—increased
 - (3) Lipemia—absent
 - f Bones (see Fig. 264)
 - (1) Osteoporosis
 - (2) Sclerosis
 - (3) Deformity especially
 - (a) Femurs
 - (b) Vertebrae
 - (4) Cotton wool appearance
 - (5) Spontaneous fractures
 - (6) Sternal puncture—typical Gaucher cells
- 2 Neumann Pick's disease^{13a}
- a Familial tendency
 - b Congenital occurrence patient rarely lives beyond 2 years
 - c Physical status
 - (1) Evidence of cachexia
 - (2) Blue black discoloration of mucous membranes of mouth
 - (3) Skin pigmentation
 - (4) Splenomegaly
 - (5) Hepatomegaly
 - (6) Lymphadenopathy
 - d Blood count
 - (1) Normomacrocytic anemia
 - (2) Leukopenia
 - (3) Platelets
 - (a) Normal
 - (b) Decreased
 - e Serum chemical analyses are normal for
 - (1) Cholesterol (plasma may be increased slightly)
 - (2) Calcium
 - (3) Phosphorus
 - (4) Alkaline phosphatase
 - f Bones show slight osteoporosis
 - g "Foam cells" in
 - (1) Blood
 - (2) Bone marrow
 - (3) Spleen
 - (4) Other tissues
- 3 Lipoid granulomatosis (Hand Schuller Christian disease)^{13b}
- a Characteristics
 - (1) Exophthalmos
 - (2) Diabetes insipidus
 - (3) Xanthomata
 - (4) No external signs in some cases
 - b Serum
 - (1) The following are normal
 - (a) Calcium
 - (b) Phosphorus
 - (c) Alkaline phosphatase
 - (2) Cholesterol (plasma)
 - (a) Normal
 - (b) Increased
 - c Bones
 - (1) Destructive areas may be found
 - (2) Punched out lesions
 - (3) Uninvolved bone is normal in texture
 - (4) Old sites may appear cystic due to fibrosis
 - (5) Spontaneous fractures
 - (6) Biopsy of fresh areas show foam cells containing cholesterol
 - (7) Lesions are radiosensitive
- ## XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES
- A SEQUELAE (these include all signs or symptoms related to bone or renal changes—see 38 VI, XIV)
- 1 Pyelitis
 - 2 Pyelonephritis
 - 3 Renal failure^{2, 3}
 - 4 Tetany, from infarction of adenoma
 - 5 Compression of spinal cord as a result of fracture or collapse of vertebrae
 - 6 Acute hyperparathyroidism
 - 7 Arterial disease^{13a}
 - 8 Metastasis⁴⁷
- B ASSOCIATED DISEASES
- 1 Acromegaly²²
 - 2 Hyperthyroidism

(d) Later concentrations return to normal

(3) Treatment

(a) When symptoms are very mild, withholding therapy may speed up function of remaining glands and hasten recovery from hypocalcemia

(b) If the tetany is moderately severe, usual measures may be employed (see 38 XVI)

(c) For severe cases constant intravenous administration of calcium may be necessary

b Oliguria

(1) Occurrence—frequent

(2) Nonprotein nitrogen—rises temporarily

(3) Treatment—hypertonic glucose and saline intravenously

c Acidosis⁸

(1) Serum

(a) Sodium—decreased

(b) Chlorides—increased

(c) Carbon dioxide combining power—decreased

(2) Treatment

(a) Sodium bicarbonate orally

(b) Sodium lactate intravenously

d Transient difficulty in focusing eyes

e Mental changes

(1) Acute psychosis

(2) Depression

(3) Treatment—may subside with management of tetany

f Paralytic ileus—a rare complication

XVII PROGNOSIS

A ACUTE HYPERPARATHYROIDISM—Disease may be rapidly fatal unless recognized early

B CHRONIC HYPERPARATHYROIDISM

1 Without surgical procedure

a Actual morbidity is not known

b Average duration of disease is 5 to 7 years

c Dependent on severity of hypersecretion

(1) Mild degree of hyperactivity with adequate vitamin D and calcium intake might be compatible with average outlook

(?) Very active disease indicates unfavorable prognosis

d Spontaneous remissions or cures are possible but probably rare⁹

e Pregnancy^{66 111 121}

(1) Normal

(2) Stillborn

(3) Infantile tetany

2 Postoperative outcome

a Renal changes

(1) If kidney function is adequate improvement after surgery should be very favorable

(2) Nephrocalcinosis is not reversible except possibly in early cases

(3) Azotemia may persist in some cases (see Chart 85)

(4) Progressive tubular impairment may cause

(a) Acidosis

(b) Failure of recalcification

b Bones

(1) Relief of pain

(2) Recalcification by calcium retention, occasionally this may not occur, due to lack of increased osteoblastic activity¹⁴

(3) Recovery may be retarded because of

(a) Menopause

(b) Senility

(c) Chronic infection

(d) Inanition

(e) Vitamin D deficiency¹⁻³

(f) Other diseases complicating picture

c Pregnant patient—mother and child normal¹¹¹

3 Recurrence after surgery

a Unlikely after removal of adenoma

b Possible recurrence with

(1) Hyperplasia

(2) Malignancy^{18 43 60}

(3) Insufficient removal

c Several years or more may be necessary to demonstrate recalcification by roentgenographic films

XVIII CAUSES OF DEATH

A ACUTE HYPERPARATHYROIDISM

B RENAL FAILURE

C INTERCURRENT INFECTION

D INCIDENTAL DISEASES

- (11) Check lower poles of thyroid, following small arterial branches from inferior thyroid artery
 - (12) If no glands are found, a wider dissection is performed from upper lobe to larynx
 - (13) Areolar tissue as far lateral as carotid sheath is inspected also
 - (14) Examine behind esophagus, although absence of vascular pedicle probably excludes presence of gland or tumor
 - (15) Carry dissection down into posterior mediastinum on either side
 - (16) Identify thoracic duct on left
 - (17) Inspect anterior mediastinum as far as direct vision is possible
 - (18) Identification of vascular pedicles may give immediate clue to location of adenoma
 - (19) Thymic rests may enclose para-thyroid tissue, inspect before removal
 - (20) Resection of whole thyroid is rarely necessary, adenoma may be palpated within thyroid
- c Exploration of mediastinum¹
- (1) Incise skin to third interspace
 - (2) Insert finger posterior to manubrium and blunt dissect space for cutting sternum
 - (3) Opening is made on one side at third interspace and pleura pushed away
 - (4) Tunnel behind manubrium to third interspace
 - (5) Sternum is cut by Lebsche knife
 - (6) Anterior mediastinum is explored on that side if no tumor other side is examined in the same way
 - (7) Search from neck down to right auricle
 - (8) The tumor may be found
 - (a) On either side of aorta in the middle of mediastinum
 - (b) Anterior or posterior to innominate vein
 - (c) Within thymus
 - (9) Suture sternum with stainless steel wire
- (10) Close without drain after all air and fluid removed from mediastinum by suction
- 4 Results (see Chart 84)
- a Serum
 - (1) Calcium falls to normal within a few days
 - (2) Phosphorus rises
 - b Improvement in general well being including correction of symptoms
 - c Recalcification of bone
 - (1) Exact percentage is unknown
 - (2) Snapper reports only 70 per cent were recalcified 10 years after operation (postmortem analyses)¹²⁰
 - (3) Many show little evidence of this, because of other factors, as menopause, senility, etc
 - d Failure to find adenoma may require a subsequent operation
- 5 Postoperative complications
- a Tetany
 - (1) General
 - (a) Occurs in 50 per cent of cases
 - (b) More likely with
 - [1] High preoperative alkaline serum phosphatase (above 20 Bu)
 - [2] Marked bone decalcification
 - (c) Severe and difficult to manage sometimes because
 - [1] Osteoblastic activity is increased
 - [2] Osteoclastic process ceases with removal of excess parathyroid secretion
 - [3] Bones will readily absorb all the available calcium or will not yield it to blood stream, due to surrounding osteoblasts⁶
 - (2) Serum
 - (a) Calcium falls quickly
 - (b) Phosphorus may decrease even when tetany is present as from osteomalacia
 - (c) Alkaline phosphatase may rise after operation

CONDITIONS	URINARY				BALANCE		GASTRO- INTESTINAL ABSORPTION		UTILIZATION		FECAL		SERUM				
	Calcium	Phosphorus	Calcium	Phosphorus	Calcium	Phosphorus	Calcium	Phosphorus	Utilization of calcium—analogs	Rejection or loss of calcium	Calcium	Phosphorus	Calcium	Phosphorus	Phosphatase	Carbon dioxide combining power	Chlorides
Sprue or steatorrhea	+	+	1	1	1	1	1	1	1 or N	1 or 2	+	+	1	1 or 2	+	1 or 2	N
Negative nitrogen balance infections or immobilization	+	+	1 or 2	1	1	1	1	1	1	1	+	+	N	1	N	N	N
Hypoparathyroidism	+	+	1	N?	1	1	1	1	1	1	1	1	+	+	N or 2	N	1
Hypoparathyritism	+	+	1	+	1	2	N or 1	N or 2	+	+	N	N	N	+	N or 2	N	N
Hypothyroidism	N	N	+	+	+	+	1	1	+	+	+	+	N	N or 2	N or 2	N	N
Hypothyroidism	+	+	1	1	1	1	1	1	+	+	+	+	N	N or 2	N or 2	N	N
Hypoadrenocorticalism	+	+	1	1	1	1	1	1	+	+	+	+	N	N or 2	N or 2	N	+
Hypogonadism	N	N	N	N	N	N	N	N	1	?	1	1	N	N	N or 2	N	N

All signs are relative amounts

0 = Absent
+ = Less than normal
N = Normal
++ = Increased

4+ = Excess
? = Questionable or unknown
V = Normal increased or decreased

[623]

All signs are relative amounts

O = Absent
 — = Less than normal
 N = Normal
 + = Increased

4+ = Excess
 ? = Questionable or unknown
 V = Normal increased or decreased

REFERENCES

- 1 Albright F. Hyperparathyroidism: its diagnosis and exclusion. *New England J Med* 209 416-480 (Sept) 1933
- 2 — Parathyroids—physiology and therapeutic J. A. M. A. 117 527-533 (Aug) 1941
- 3 — Conference on Metabolic Aspects of Calcium Metabolism Including Bone and Wound Healing 1st Meeting Sept. New York, Josiah Macy Jr. Foundation 1942 p 25
- 4 — Conference on Metabolic Aspects of Calcium Metabolism Including Bone and Wound Healing 5th Meeting Oct. 8-9 New York, Josiah Macy Jr. Foundation 1943 p 98
- 5 — Conference on Metabolic Aspects of Calcium Metabolism Including Bone and Wound Healing 10th Meeting June 15-16 New York, Josiah Macy Jr. Foundation 1945 p 310
- 6 *Ibid* p 312
- 7 — Polyostotic fibrous dysplasia: defense of entity. *J Clin Endocrinol* 7 307-324 (May) 1947
- 8 — Osteoporosis. *Ann Int Med* 27 861-882 (Dec) 1947
- 9 Albright F., Baird P. C., Cope O. and Bloomberg E. Studies on physiology of parathyroid glands: renal complications of hyperparathyroidism. *Am. J. M. Sc.* 187 49-65 (Jan) 1934
- 10 Albright F., and Bloomberg E. Hyperparathyroidism and renal disease. *Tr Am A Genito-Urin Surgeons* 27 195-202 1934
- 11 Albright F., Bloomberg E., Castleman B. and Churchill E. D. Hyperparathyroidism due to diffuse hyperplasia of all parathyroid glands rather than adenoma of one: clinical studies on 3 cases. *Arch Int Med* 54 315-329 (Sept) 1934
- 12 Albright F., Burnett C. H., Cope O. and Parson W. Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism. *J Clin Endocrinol* 1 711-716 (Sept) 1941
- 13 Albright F., Burnett C. H., Parson W., Reifenstein E. C. Jr. and Roos A. Osteomalacia and late rickets. *Medicine* 25 399-479 (Dec) 1946
- 14 Albright F., Butler A. M., Hampton A. O. and Smith P. H. Syndrome characterized by osteitis fibrosa disseminata areas of pigmentation and endocrine dysfunction, with precocious puberty in females: report of 5 cases. *New England J Med* 216 727-746 (Apr) 1937
- 15 Albright F., Drake T. G. and Sulkowitch H. W. Renal osteitis fibrosa cystica: report of a case with discussion of metabolic aspect. *Bull Johns Hopkins Hosp* 60 377-399 (June) 1937
- 16 Albright F. and Reifenstein E. C. Jr. The Parathyroid Glands and Metabolic Bone Disease. Baltimore: Williams & Wilkins 1948 p 47
- 17 *Ibid* pp 49-50
- 18 *Ibid* p 51
- 19 *Ibid* p 57
- 20 *Ibid* p 62
- 21 *Ibid* p 71
- 22 *Ibid* p 77
- 23 *Ibid* p 97
- 24 *Ibid* p 98
- 25 *Ibid* p 101
- 26 *Ibid* p 106
- 27 *Ibid* p 113
- 28 *Ibid* p 118
- 29 *Ibid* p 145
- 30 *Ibid* p 218
- 31 Albright F., Seaville W. B., and Sulkowitch H. W. Syndrome characterized by osteitis fibrosa disseminata areas of pigmentation and gonadal dysfunction. *Endocrinology* 22 411-421 (Apr) 1938
- 32 Albright F., Smith P. H., and Richardson A. M. Postmenopausal osteoporosis: clinical features. *J. A. M. A.* 116 2465-2474 (May) 1941
- 33 Alexander H. B., Kepler E. J., Pemberton J. de J. and Broders, A. C. Functional parathyroid tumors and hyperparathyroidism. *Am. J. Surg* 65 157-183 (Aug) 1944
- 34 Andersen D. H. and Schlesinger M. R. Renal hyperparathyroidism with calcification of arteries in infancy. *Am J Dis Child* 63 302-325 (Jan) 1942
- 35 Anderson J. P. Hereditary Gaucher's disease. *J. A. M. A.* 101 979-981 (Sept) 1933
- 36 Anderson W. A. D. Hyperparathyroidism and renal disease. *Arch Path.* 27 753-758 (Apr) 1939
- 37 Bailes, G. H., Barclay J. A. and Cooke W. T. Nephrocalcinosis associated with hyperchloremia and low plasma bicarbonate. *Quart J Med* 14 113-123 (Apr) 1940
- 38 Bartick E. C., and Kimmel C. B. Metastatic carcinomas simulating hyperparathyroidism. *Ann Int. Med* 13 144-1752 (Mar) 1940
- 39 Bauer W., Albright F. and Aub J. C. Case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of parathyroid bodies: metabolic study. *J. Clin. Investigation* 8 229-248 (Feb) 1930
- 40 Belden W. W. Bone diseases. *Radiology* 11 281-314 (Oct) 1928
- 41 Bellin H. E. and Gershwin B. S. Hyperparathyroidism with renal insufficiency. *Am J M Sc* 190 519-525 (Oct) 1935
- 42 Best C. H. and Taylor N. B. The Physiological Basis of Medical Practice, ed 3. Baltimore: Williams & Wilkins 1943 p 107
- 43 Black H. M. Adenocarcinoma of parathyroid origin with hyperparathyroidism, local recurrence and metastases: report of a case. *Proc. Staff Meet. Mayo Clin* 23 8-14 (Jan) 1943
- 44 — Surgical aspects of hyperparathyroidism: review of 63 cases. *Surg Gynec & Obst* 87 172-182 (Aug) 1948
- 45 Black H. M. and Sprague R. G. Hyperparathyroidism due to diffuse primary hypertrophy and hyperplasia of parathyroid glands. *Proc Staff Meet. Mayo Clin* 22 3-30 (Feb) 1947
- 46 Borah, J. and Doll H. Halbseltene Recklinghausen'sche Knochenkrankheit mit Pubertas praecox. *Wien Klin Wochenschr* 47 540 (Apr) 1934
- 47 Burk, L. B. Hyperparathyroidism: an analysis of ten cases with special reference to earlier diagnosis. *Am J Surg* 76 404-411 (Oct) 1948
- 48 Cantarow A. and Hare H. A. Calcium metabolism and calcium therapy. Philadelphia: Lea & Febiger 1933 p 102
- 49 Cantarow A., Hawry V. M. and Whitebell, C. G. Effect of parathyroid hormone on diffusion of calcium, magnesium and phosphorus into peritoneum. *Proc Soc. Exper Biol. & Med.* 39 15-17 (Oct.) 1938

HYPERPARATHYROIDISM⁵⁰

PROTOCOL XXVIII FIG 261

Secondary Hyperparathyroidism with Calcinosis, Probably Due to
Renal Disease and Excess Ingestion of Vitamin D

Family history Tuberculosis

Past medical Patient well until 5 years ago

Chief complaints Pain in the legs and right shoulder for 7 months

History of present illness

YEARS

- 5 Frontal headaches, anorexia, weakness, thirst, nocturia and urgency Albuminuria
- 4½ Edema of ankles in the evening and puffiness around the eyes in the morning
- 1 Drank 1 to 2 milk shakes daily, and later 1 to 2 quarts of milk daily Vitamin D taken in large doses for 1 year

MONTHS

- 8 Severe diarrhea for 6 weeks with a weight loss of 15 lbs
- 7 Several large lumps, 6 to 8 in in diameter, appeared on his shoulders, left arm and both thighs A few months later a mass developed in right axilla
- 5 Dyspnea and severe pain with exertion in thighs hips and sacrum Biopsy of one of the masses showed calcinosis

Physical examination Age 33, male, single Extreme pallor, evidence of weight loss uremic breath, but alert Weight 121¼ lbs Height 64¾ in Pulse 90 BP 144/94 Skin coarse and dry Buccal mucosa, palms and nail beds pale Cauliflower shaped tender resilient 5 x 6 in to 6 x 8 in masses, apparently present in the muscle over the deltoids, tensor fasciae latae right trapezius crest and right axilla Liver palpable at costal margin and tender Right testis was small, soft and tender Prostate gland enlarged to twice the normal size and felt boggy Optic disks arteriosclerosis, Grade II Radial vessels rigid and beaded Reflexes hyperactive Chvostek's sign positive on left

Laboratory data Urine—specific gravity 1.015, albumin 2 plus, sediment 20 to 40 WBC, Sulkowitch test negative, culture hemolytic staphylococcus aureus RBC 2,990,000 Hgb 9.6 Gm WBC 9,750

Differential polymorphonuclears 85.0%, band forms 0.5%, lymphocytes 11.0%, monocytes 1.5%, eosinophils 3.0% Hematocrit 28% NPN 113, 102, 115 and 129 mg % Total protein 9.0 Gm %, albumin 4.5 Gm %, globulin 4.5 Gm %, A/G ratio 1.1 Plasma cholesterol 115 mg % Serum calcium 11.1 mg % Serum phosphorus 8.8 mg % Serum phosphatase alkaline 6 B u, acid 0.3 units (normal) Serum chlorides 561 mg % Carbon dioxide combining power 21 volumes % Water test positive Sedimentation rate 115 mm/hr Bromsulphalein 5% dye retention in 1 hr Cephalin flocculation negative Urea clearance 8% of normal Calcium balance studies diet 0.099 to 0.1 Gm of calcium daily for 5 days urine calcium was low in view of the marked renal impairment

Röntgenographic findings Skull—osteoporotic changes consistent with hyperparathyroidism Shoulders and hips—masses of calcification in soft tissues surrounding, but not involving the hip and shoulder joints Marked calcification of arteries in both shoulder areas, throughout the pelvis, aortic knob, hands and abdomen Long bones normal Pyelogram IV—no excretion on either side in 1½ hrs retrograde—kidneys were small, and their outlines well visualized, the pelves and calices of both were normal with good cortical margins bilaterally Esophagus normal, with no evidence of a mediastinal mass on fluoroscopic examination

Treatment Blood transfusion 500 cc Low phosphorus diet with protein 70 Gm a day Amphojel 2 teaspoonfuls before and after meals and at bedtime Three liters of fluid daily, including 1 pint of milk

Progress Patient stated at a later date that metastatic calcifications were disappearing but eventually he died

Comment A case of marked renal impairment and associated metastatic calcinosis resulting from altered phosphorus and calcium metabolism The excessive intake of vitamin D may have been a factor in the renal insufficiency Metastatic calcifications have been reported in cases of vitamin D toxicity

- universals *Acta med Scandinav* 127 53 64 (Mar) 1947
- 91 Levy M S Power M H and Kepler E J Specificity of water test as diagnostic procedure in Addison's disease *J Clin Endocrinol* 6 607 632 (Sept) 1946
- 92 Lichtenstein L Polystotic fibrous dysplasia *Arch Surg* 36 874 893 (May) 1938
- 93 Lichtenstein L and Jaffe H L Fibrous dysplasia of bone condition affecting one several or many bones graver cases of which may present abnormal pigmentation of skin premature sexual development hyperthyroidism or still other extraskeletal abnormalities *Arch Path* 33 777 816 (June) 1942
- 94 Linden O Case of osteitis fibrosa generalisata with well marked tendency to spontaneous cure *Acta radiol* 15 202 209 1934
- 95 Looser E Über pathologische Formen von Infractionen und Callus bildungen bei Rachitis und Osteomalakie und anderen knöchernen Krankheiten *Zentralbl f Chir* 47 14 0 1474 (Nov) 1920
- 96 — Late rachitis and osteomalacia clinical roentgenologic and pathologic anatomic investigations *Deutsche Zeitschr f Chir* 152 210 1920
- 97 McClure H D and Lam C R End results in treatment of hyperparathyroidism *Ann Surg* 121 454 469 (Apr) 1945
- 98 McCune D J Mason H H and Clarke H T Intracapsular hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome) report of case in which increased urinary organic acids were detected and identified with review of literature *Am J Dis Child* 81 146 (Jan) 1943
- 99 Mellgren J Acute fatal hyperparathyroidism *Acta path et microbiol Scand* 20 693 734 1943
- 100 Meyer K A Ross P A and Ragins A B Carcinoma of parathyroid gland *Surgery* 6 190-200 (Aug) 1939
- 101 Mulkhan L A Pseudofractures (hunger osteopathy late rickets osteomalacia) report of case *Am J Roentgenol* 24 29 37 (July) 1930
- 102 — Multiple spontaneous idiopathic symmetrical fractures *Am J Roentgenol* 32 622 634 (Nov) 1934
- 103 Murray R C Kirkpatrick H J R and Forrai E Case of Albright's syndrome (osteitis fibrosa disseminata) *Brit J Surg* 34 48 37 (July) 1946
- 104 Neller J L Osteitis fibrosa cystica (Albright) *Am J Dis Child* 61 590-605 (Mar) 1941
- 105 Norris E H Anatomical evidence of prenatal function of the human parathyroid glands *Anat Rec* 96 129 141 (Oct) 1946
- 106 — The parathyroid adenoma *Internat Abstr Surg* 84 1 41 (Jan) 1947
- 107 — Carcinoma of parathyroid glands *Internat Abstr Surg* 86 1 21 (Jan) 1948
- 108 Oliver W A Acute hyperparathyroidism *Lancet* 2 240-244 (July) 1939
- 109 Orr J quoted by Albright F and Howard J E Conference on Metabolic Aspects of Conalescence Including Bone and Wound Healing 1st Meeting Sept New York Josiah Macy Jr Foundation 1942 p 36
- 110 Patt H M and Luckhardt A B Relationship of low blood calcium to parathyroid secretion *Endocrinology* 31 384 392 (Sept) 1942
- 111 Peck F H and Sage C V Diabetes mellitus associated with Albright's syndrome (osteitis fibrosa disseminata) areas of skin pigmentation and endocrine dysfunction with precocious puberty in females *Am J M Sc* 208 35-46 (July) 1944
- 112 Perl D and Hunter L Nephrosis in multiple myeloma *Am J Path* 21 285 298 (May) 1930
- 113 Pettit D W and Clark R L Jr Hyperparathyroidism and pregnancy *Am J Surg* 74 860 866 (Dec) 1947
- 114 Pope A and Aub J C Medical progress parathyroid glands and parathormone *New England J Med* 230 698 07 (June) 1944
- 115 Pratt E L Geren B H and Neuhauser E B D Hypercalcemia and idiopathic hyperplasia of parathyroid glands in an infant *J Pediatr* 30 388 399 (Apr) 1947
- 116 Reifstein M C Jr Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 3rd Meeting March New York Josiah Macy Jr Foundation 1943 p 33
- 117 Rieckel C Royster H P Gislason E J., and Hughes P E Chemical studies in hyperparathyroidism and urolithiasis *J Urol* 57 192 195 (Jan) 1947
- 118 Rogers H M Parathyroid adenoma and hypertrophy of parathyroid glands *JAMA* 130 22 28 (Jan) 1946
- 119 Rogers H M and Keating F R., Jr Primary hyperthyroidism and hyperplasia of the parathyroid glands as a cause of hyperparathyroidism *Am J Med* 3 384 401 (Oct) 1947
- 120 Rogers H M Keating F R., Jr Morlock C G and Barker N W Primary hyperthyroidism and hyperplasia of the parathyroid glands associated with duodenal ulcer report of an additional case with special reference to metabolic gastrointestinal and vascular manifestations *Arch Int Med* 79 307-321 (Mar) 1947
- 121 Rowntree L G Progress relative to diseases of ductless glands *Pennsylvania M J* 36 646 660 (June) 1933
- 122 Schmorl G Fibrous osteitis osteomalacia and rickets comment on Lang's article *Klin Wchnschr* 5 496-497 (Mar) 1926
- 123 Shirer J W Duncan W and Haden R L Hyperproteinemia due to Bence Jones protein in myelomatosis *Arch Int Med* 50 829 835 (Dec) 1932
- 124 Shorr E Conference on Metabolic Aspects of Conalescence Including Bone and Wound Healing 4th Meeting June 12 12 New York Josiah Macy Jr Foundation 1943 p 74
- 125 Snapper I Medical Clinics on Bone Diseases *New York Interscience* 1943 p 14
- 126 *Ibid* p 21
- 127 *Ibid* p 22
- 128 *Ibid* p 29
- 129 *Ibid* p 52
- 130 *Ibid* p 54
- 131 *Ibid* p 64
- 132 *Ibid* p 73
- 133 Stander H J and Ahearn R E Hyperparathyroidism in pregnancy *J Mt Sinai Hosp* 14 629 633 (Sept Oct) 1947
- 134 Stephenson H U Jr McNamara W L and Goldberg H The parathyroid a study based in part on 60 postmortem examinations with presentation of a case of hyperfunctioning

- 50 Castleman B and Mallory T B The pathology of the parathyroid gland in hyperparathyroidism: study of 25 cases *Am J Path* 11 1 72 (Jan) 1935
- 51 Cattell R B Personal communication
- 52 Chasnoff J Friedfeld, L and Tunick A M Hyperparathyroidism in patient with acromegaly *Ann Int Med* 16 162 175 (Jan) 1942
- 53 Compere E L Pathologic and biochemical changes in skeletal dystrophies *Arch Surg* 32 232 272 (Feb) 1936
- 54 Cook E N and Keating F R Jr Renal calculi associated with hyperparathyroidism *J Urol* 54 525 530 (Dec) 1945
- 55 Cope O Surgery of hyperparathyroidism: the occurrence of parathyroids in the anterior mediastinum and the division of the operation into stages *Ann Surg* 114 66 733 (Oct) 1941
- 56 — Hyperparathyroidism: significance of generalized hyperplasia: report of eleven cases *Clinics* 1 1163 1178 (Feb) 1943
- 57 — Endocrine aspect of enlargements of parathyroid glands *Surgery* 16 273 288 (Aug) 1944
- 58 Couch J H and Robertson H F Occurrence of postoperative acidosis and pagetoid bone changes in hyperparathyroidism *Surg Gynec & Obst* 73 165 175 (Aug) 1941
- 59 Curtis G M and Fertman M B Blood iodine studies: blood iodine in nonthyroid disease *Arch Surg* 54 541 554 (May) 1947
- 60 Dawson J W and Struthers J W Generalized osteitis fibrosa with parathyroid tumour and metastatic calcification including a critical discussion of pathological processes underlying osseous dystrophies *Edinburgh M J* 30 421 564 (Oct) 1923
- 61 de Wesselow O L V and Wardener H E Carcinoma of the parathyroid gland with hyperparathyroidism *Lancet* 1 820 823 (May) 1949
- 62 Dockerty M B Myerding H W and Wallace G T Albright's Syndrome: Fibrous Dysplasia of Bones with Cutaneous Pigmentation in Both Sexes and Gonadal Dysfunction in Females *Medical Clinics on Bone Diseases* New York Interscience 1943 pp 1 225
- 63 Falconer M A Cope C L and Robb Smith A H T Fibrous dysplasia of bone with endocrine disorders and cutaneous pigmentation (Albright's disease) *Quart J Med* 11 121 154 (July) 1942
- 64 Fleischner F G and Shalek S R Conjunctival and corneal calcification in hypercalcemia *New England J Med* 241 863 865 (Dec) 1949
- 65 Fretheim B and Lange H F Carcinoma of parathyroid with hyperparathyroidism *Acta endocrinol* 1 203 216 1948
- 66 Freund E Zur Frage der Ostitis deformans Paget Virchow's *Arch f Path and Anat* 274 1 36 (Nov) 1930
- 67 Goldhamer K Osteodystrophia fibrosa unilateralis (kombiniert mit Pubertas praecox und mit gleichseitigen osteo-klerotischen Veränderungen des Schädels) *Fortschr a d Geb d Röntgenstrahlen* 49 456 481 (May) 1934
- 68 Gorham L W Campbell E H Howard W P Donhauser J L and Rust N H Albright's syndrome, a group of cases characterized by osteitis fibrosa disseminata: areas of pigmentation and a gonadal dysfunction *Clinics* 1 358 385 (Aug) 1942
- 69 Graybiel A., and White P D Electrocardiography in Practice Philadelphia Saunders 1941 p 106
- 70 Gutman A B quoted by Snapper I *Medical Clinics on Bone Diseases* New York Interscience 1943 p 19
- 71 Gutman A B Tyson T L and Gutman E B Serum calcium inorganic phosphorus and phosphatase activity in hyperparathyroidism: Paget's disease, multiple myeloma and neoplastic disease of bones *Arch Int Med* 57 379-413 (Feb) 1936
- 72 Haines S F Hyperparathyroidism due to parathyroid adenoma with death from parathyroid intoxication *Am J M Sc* 197 85 90 (Jan) 1939
- 73 Hanno R R Shorr E McClellan W S and DuBois E F Case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of parathyroid bodies: metabolic study *J Clin Investigation* 8 215 227 (Feb) 1930
- 74 Hansen A E Phosphatase activity of serum and tissues in osteogenesis imperfecta *Proc Soc Exper Biol & Med* 31 1023 1025 (May) 1934
- 75 Howard J E Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 2nd Meeting Dec New York Josiah Macy Jr Foundation 1942 p 88
- 76 Howard J E and Wilkins L quoted by Albright F Burnett C H Cope O and Parson W Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism *J Clin Endocrinol* 1 711 716 (Sept) 1941
- 77 Jacobson B M and Milner L R Detection of urinary Bence Jones protein *Am J Clin Path* 11 133 149 (Mar) 1944
- 78 Jaffe H L Hyperparathyroidism (Recklinghausen's Disease of Bone) *Arch Path* 11 63 112 (July) 236 258 (Aug) 1933
- 79 — Hyperparathyroidism *Bull New York Acad Med* 16 291 311 (May) 1940
- 80 Kaufman M and Dow J W Hyperparathyroidism with calcinosis probably secondary to renal disease *Lahey Clin Bull* 5 21 26 (July) 1946
- 81 Keating F R Jr and Cook E N The recognition of primary hyperparathyroidism *JAMA* 129 994 1002 (Dec) 1945
- 82 Keating F R Jr Hyperparathyroidism *Am J Orthodontics (Oral Surg Sect)* 33 116 128 (Feb) 1947
- 83 Kellogg F and Kerr W J Electrocardiographic changes in hyperparathyroidism *Am Heart J* 12 346-351 (Sept) 1936
- 84 Kesen M and Bakst H Co existing myxedema and hyperparathyroidism: case report *J Clin Endocrinol* 7 152 158 (Feb) 1947
- 85 Kleneshoj N C and Koepf G F Serum phosphatase activity in hyperparathyroidism *J Clin Endocrinol* 3 351 352 (June) 1943
- 86 Kornblum K Polyostotic fibrous dysplasia *Am J Roentgenol* 46 145 159 (Aug) 1941
- 87 Lahey F H and Haggart G E Hyperparathyroidism: clinical diagnosis and operative technique of parathyroidectomy *Surg Gynec & Obst* 60 1033 1051 (June) 1935
- 88 Lebel H and Madden A R Case of calcinosis



FIG 245 HYPERPARATHYROIDISM (See also Figs 246 251 254 and 255) Age 61 Hyperparathyroidism due to substernal parathyroid adenoma. Picture taken 6 months after removal of adenoma. Note dorsal round back and chest deformity (Lahey F H and Haggart G E. Hyperparathyroidism: clinical diagnosis and operative technique of parathyroidectomy. Surg Gynec & Obst 60 1033 1051)



FIG 246 HYPERPARATHYROIDISM (See also Figs 245 251 254 and 255) Skull in hyperparathyroidism. Note thickening of both tables of the skull and the fuzzy appearance indicating marked osteoblastic activity (Lahey F H and Haggart G E. Hyperparathyroidism: clinical diagnosis and operative technique of parathyroidectomy. Surg Gynec & Obst 60 1033 1051)



FIG 247 SKULL IN HYPERPARATHYROIDISM. Note thinning of tables at top of skull and mottled appearance

- adenoma *Am J Med Sc* 215 381 397 (Apr) 1948
- 133 Stephenson H U Jr Malignant tumors of the parathyroid glands *Arch Surg* 60 247 266 (Feb) 1950
- 134 Stobie H H Hyperparathyroidism *Canad M A J* 57 233 237 (Sept) 1947
- 135 Strock M S Mouth in hyperparathyroidism *New England J Med* 224 1019 1023 (June) 1941
- 136 Thannhauser, S J *Lipiodoses Diseases of the Cellular Lipid Metabolism* London and New York Oxford Med Publications 1940 p 129
- 137 *Ibid*, pp 265 322
- 138 *Ibid* p 325
- 139 — Neurofibromatosis (von Recklinghausen) and osteitis fibrosa cystica localisata et disseminata (von Recklinghausen) study of common pathogenesis of both diseases *Medicine* 23 105 149 (May) 1944
- 140 Ullmann T M and Schorr S Renal dwarfism with hyperparathyroidism in case of congenital familial malformation of kidneys, *Ann Int Med* 29 715 730 (Oct) 1948
- 141 Vaughan J H Soiman M C and Kinsley T D Nephrocalcinosis, *Radiology* 58 33-4, (July) 1947
- 142 Voltz C P., and Smull K. Hyperparathyroidism with failure of recalcification after removal of parathyroid adenoma, *Ann Int Med.* 21 329 332 (Aug) 1944
- 143 Walsh F M and Howard J E Conjunctival and corneal lesions in hypercalcemia, *J Clin Endocrinol.* 7 644 652 (Sept) 1947
- 144 Warren S and Morgan J R E Parathyroid glands histologic study of parathyroid adenoma *Arch Path* 20 823 836 (Dec.) 1935
- 145 Wilder R M Hyperparathyroidism tumor of parathyroid glands associated with osteitis fibrosa *Endocrinology* 13 231 244 (May June) 1929
- 146 Wild R M and Howell L P Etiology and diagnosis in hyperparathyroidism review of 150 proved cases, *J.A.M.A.* 106 427-431 (Feb) 1936



FIG 245 HYPERPARATHYROIDISM (See also Figs 246 251 254 and 255) Age 61 Hyperparathyroidism due to sub-sternal parathyroid adenoma. Picture taken 6 months after removal of adenoma. Note dorsal round back and chest deformity (Lahay F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)



FIG 246 HYPERPARATHYROIDISM (See also Figs 245 251 254 and 255) Skull in hyperparathyroidism. Note thickening of both tables of the skull and the fuzzy appearance indicating marked osteoblastic activity (Lahay F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)



FIG 247 SKULL IN HYPERPARATHYROIDISM. Note thinning of tables at top of skull and mottled appearance

- adenoma *Am J Med Sc* 215 381 397 (Apr) 1948
- 133 Stephenson H U Jr. Malignant tumors of the parathyroid glands *Arch Surg* 60 247 266 (Feb) 1950
- 134 Stobie G H. Hyperparathyroidism *Canad M A J* 57 233 237 (Sept) 1947
- 135 Strock M S. Mouth in hyperparathyroidism *New England J Med* 224 1019 1023 (June) 1941
- 136 Thannhauser S J. *Lipidoses: Diseases of the Cellular Lipid Metabolism*, London and New York Oxford Med Publications 1940 p 149
- 137 *Ibid* pp 365 322
- 138 *Ibid* p 323
- 139 —. Neurofibromatosis (von Recklinghausen) and osteitis fibrosa cystica localisata et diseminata (von Recklinghausen): study of common pathogenesis of both diseases *Medicine* 23 105 149 (May) 1944
- 140 Ullmann T D and Schorr S. Renal dwarfism with hyperparathyroidism in case of congenital familial malformation of kidneys *Ann Int Med* 29 715 730 (Oct) 1948
- 141 Vaughan J H Sosman M C and Kinney T D. Nephrocalcinosis *Radiology* 58 33 45 (July) 1947
- 142 Voltz C P and Smull K. Hyperparathyroidism with failure of recalcification after removal of parathyroid adenoma *Ann Int Med* 21 329 332 (Aug) 1944
- 143 Walsh F W and Howard J E. Conunctival and corneal lesions in hypercalcemia *J Clin Endocrinol* 7 644 652 (Sept) 1947
- 144 Warren S and Morgan J R E. Parathyroid glands, histologic study of parathyroid adenoma *Arch Path* 20 823 836 (Dec) 1935
- 145 Wilder R M. Hyperparathyroidism tumor of parathyroid glands associated with osteitis fibrosa *Endocrinology* 13 231 244 (May June) 1929
- 146 Wilder R M and Howell L P. Etiology and diagnosis in hyperparathyroidism: review of 135 proved cases *JAMA* 106 427-431 (Feb) 1936

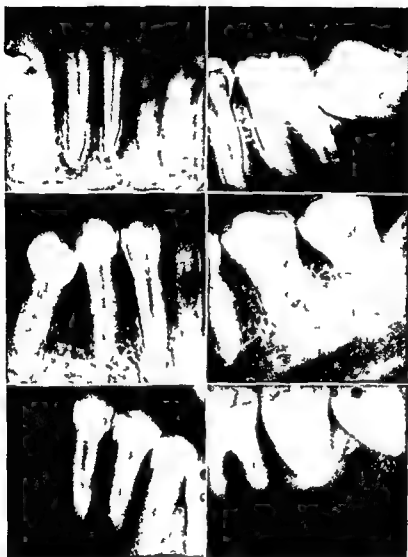


FIG 248 LAMINA DURA The disappearance of this structure occurs in hyperparathyroidism (primary or secondary) with generalized skeletal decalcification. It is not pathognomonic of hyperparathyroidism since it may occur occasionally in osteoporosis and possibly with extensive periodontal infection. The presence of the lamina dura does not exclude hyperparathyroidism. (*Top left and right*) Normal lamina dura (peridontal membrane) is demonstrated very well. (*Middle left and right*) Partial loss of lamina dura in a case of hyperparathyroidism. (*Bottom left and right*) Complete loss of lamina dura in case of hyperparathyroidism.

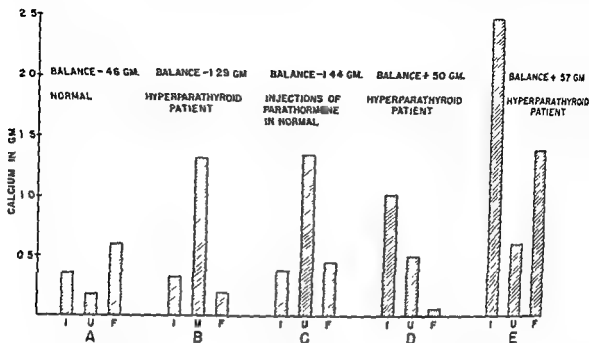


CHART 83 CALCIUM BALANCES IN THE NORMAL PERSON THE NORMAL TREATED WITH PARATHYROID EXTRACT AND HYPERPARATHYROIDISM (I = intake U = urinary calcium F = fecal calcium) (A) Normal human on low calcium intake (0.3 Gm) showing relationship between urinary and fecal excretion. Note that there is a negative balance the body drawing on its reserves for calcium. (B) Hyperparathyroidism on 0.3 Gm of calcium daily. Observe the greater negative calcium balance. Urinary output is increased and better absorption may have taken place in the gastro intestinal tract. (C) Induced hyperparathyroidism in a normal person by injection of parathyroid extract. Note similarity to (B). (D) Hyperparathyroidism on an essentially normal calcium intake. Note that calcium loss is avoided when adequate intake is supplied in this experiment. (E) Hyperparathyroidism on large calcium intake. Note that urinary output of calcium is not increased and that greater amounts of calcium are unabsorbed. It would appear in this case that maximum absorption had occurred. Contrast with calcium output in tetany on large intake of calcium (Bauer W Albright F and Aub J C Studies of calcium and phosphorus metabolism II The calcium excretion of normal individuals on a low calcium diet including data on a case of pregnancy J Clin Investigation 7 75 96 Albright F Bauer W Ropes M and Aub J C Studies of calcium and phosphorus metabolism IV The effects of the parathyroid hormone J Clin Investigation 7 139 181 Bauer E Albright F and Aub J C A case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of the parathyroid bodies Metabolic study II J Clin Investigation 8 229 258)



FIG 252 DORSAL SPINE IN HYPERPARATHYROIDISM Note almost complete compression of one dorsal vertebra (A) and herniation of nucleus pulposus (B) (verified case)



FIG 253 PELVIS IN HYPERPARATHYROIDISM Cystic areas are numerous in both iliac as well as in other parts (verified case)



FIG 254 HYPERPARATHYROIDISM Tibia and fibula in advanced hyperparathyroidism Note marked deformity, cystic areas involving most of the bone Parathyroid tumor found within lobe of thyroid gland



FIG 249 SKULL IN HYPERPARATHYROIDISM Note cystic area (epulis) in left mandible (verified case) These are often noted in dental films as the first evidence of the disease



FIG 250 CHEST IN HYPERPARATHYROIDISM (See Figs 245 246 251 and 255) Note sagging ribs The rounded shadow in the hilum proved to be the adenoma



FIG 251 DORSAL SPINE IN HYPERPARATHYROIDISM (See also Figs 245 246 250 and 255) Note decalcification and wedging of vertebrae The codfish vertebrae i.e. the concavity produced by expansion intervertebral of nucleus pulposus against softened vertebrae is well shown (Lahay F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)

FIG 258 FIBROCYSTIC OSTEITIS The cellular bone marrow is completely replaced by fibrous tissue. The remnants of the bone trabeculae are surrounded by islands of multinuclear osteoclasts. After removal of parathyroid adenomas the latter are quickly replaced by osteoblasts. (Snapper I. Medical Clinics on Bone Diseases. New York: Interscience, p. 22).



FIG 259 OSTEOMALACIA ASSOCIATED WITH RHEUMATOID ARTHRITIS POOR CALCIUM ABSORPTION AND CARCINOMA OF PANCREAS

Chief complaint Muscle weakness for 4 years

History of present illness Always well. No dietary deficiencies. Pain in knees and ankles noted for 3 years. Exploratory abdominal operation performed elsewhere was negative. Long convalescence. Tetany attacks began 3 years previously. One year before admission struck by a truck and fractured his pelvis. Nocturia.

Physical examination Age 36, male. Weight 100 lbs. Height 61½ in. BP 85/60. Pulse 104. Asthenic, chronically ill man requiring crutches to walk. Pitting edema of ankles and local heat. Slight dorsal kyphosis. Chvostek's and Trousseau's signs positive.

Laboratory data Urine: albumin trace; sugar negative; specific gravity 1.021; reaction alkaline; sediment 1 to 3 WBC. Sulkowitch test negative. RBC 4,260,000. Hgb 89 Gm. WBC 5,500. Differential normal. Hinton negative. NPN 18 mg. Total serum protein 5.9 to 6.4 Gm. albumin 3.2 Gm. and globulin 3.2 Gm. Serum calcium 6.6 and 8 mg. Serum phosphorus 1.2 and 1.1 mg. Serum sodium 140 mEq/l. Serum potassium 19.5 mg. Serum amylase 119 units. Sedimentation rate 35 mm in 1 hr. Intravenous injection of 20 cc calcium gluconate before injection serum calcium—8 mg. 10 min after 8 mg. 40 min after 7 to 8 mg. 60 min after 7.2 mg.

Röntgenographic findings Skull—thin vault with marked calcium loss and definite platybasia (from soft bones). Lamina dura barely visible. Ankles and

feet—marked decalcification and edema of tissues. Transverse fracture of tibia. **Comment** Patient died elsewhere before therapy was initiated. Postmortem revealed carcinoma of pancreas. Parathyroids were not identified, eliminating in all probability parathyroid hyperplasia.





FIG 249 SKULL IN HYPERPARATHYROIDISM Note cystic area (epulis) in left mandible (verified case) These are often noted in dental films as the first evidence of the disease



FIG 250 CHEST IN HYPERPARATHYROIDISM (See Figs 245 246 251 and 255) Note sagging ribs The rounded shadow in the hilum proved to be the adenoma



FIG 251 DORSAL SPINE IN HYPERPARATHYROIDISM (See also Figs 245 246 250 and 255) Note decalcification and wedging of vertebrae The codfish vertebrae i.e. the concavity produced by expansion inter vertebral of nucleus pulposus against softened vertebrae is well shown (Lacey F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)

FIG. 258 FIBROCYSTIC OSTEITIS The cellular bone marrow is completely replaced by fibrous tissue. The remnants of the bone trabeculae are surrounded by islands of multinuclear osteoclasts. After removal of parathyroid adenomas the latter are quickly replaced by osteoblasts (Snapper I Medical Clinics on Bone Diseases New York Interscience # 22)



FIG. 259 OSTEOMALACIA ASSOCIATED WITH RHEUMATOID ARTHRITIS POOR CALCIUM ABSORPTION AND CARCINOMA OF PANCREAS

Chief complaint Muscle weakness for 4 years

History of present illness Always well No dietary deficiencies. Pain in knees and ankles noted for 3 years. Exploratory abdominal operation performed elsewhere was negative. Long convalescence. Tetany attacks began 3 years previously. One year before admission struck by a truck and fractured his pelvis Nocturia.

Physical examination Age 36 male Weight 100 lbs Height 61½ in. BP 85/60 Pulse 104 Asthenic, chronically ill man requiring crutches to walk. Pitting edema of ankles and local heat. Slight dorsal kyphosis. Chvostek's and Trousseau's signs positive.

Laboratory data Urine albumin trace sugar negative specific gravity 1.021 reaction alkaline sediment 1 to 3 WBC. Sulkowitch test negative RBC 4,760,000 Hgb 89 Gm % WBC 5,000 Differential normal Hinton negative NPN 18 mg % Total serum protein 5.9 to 6.4 Gm % albumin 3.2 Gm % and globulin 3.2 Gm % Serum calcium 6.6 and 8 mg % Serum phosphorus 1.2 and 1.1 mg % Serum sodium 140 mEq/l Serum potassium 19.0 mg % Serum amylase 119 units Sedimentation rate 30 mm in 1 hr Intravenous injection of 20 cc calcium gluconate before injection serum calcium—8 mg % 10 min after 8 mg % 40 min after 10 mg % 60 min after 12 mg %

Röntgenographic findings Skull—thin vault with marked calcium loss and definite platybasia (from soft bones) Lamina dura barely visible Ankles and

feet—marked decalcification and edema of tissues Transverse fracture of tibia
Comment Patient died elsewhere before therapy was initiated Postmortem revealed carcinoma of pancreas Parathyroids were not identified eliminating in all probability parathyroid hyperplasia





FIG 255 PARATHYROID ADENOMA (See also Figs 245 246 251 and 254) The darkest staining cells are oxyphils. The medium staining cells are the chief cells. Those with clear cytoplasm are the wasserhelle cells.



FIG 257 NORMAL BONE Microphotograph of normal bone with concentric bone layers. The bone marrow is cellular and does not contain fibrous tissue (Snapper I. Medical Clinics on Bone Diseases New York Interscience p 22)

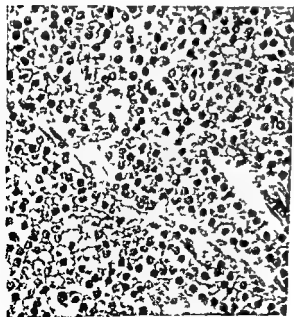


FIG 256 PARATHYROID ADENOMA Wasserhelle cell parathyroid adenoma. Note the water clear cytoplasm which distinguishes this type of parathyroid adenoma (x 300)



FIG 262 MULTIPLE MYELOMA OF THE SKULL



FIG 263 PAGET'S DISEASE Age 41 male No symptoms other than occasional spells of vertigo and slight impairment of hearing Serum alkaline phosphatase is increased in these cases with normal serum calcium and phosphorus Osteolytic phase present

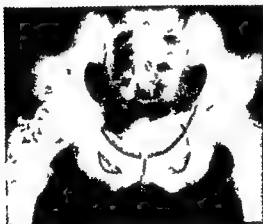


FIG 64 POLYOSTOTIC FIBROUS DYSPLASIA Age 25 male Uninvolved bone is normal in appearance No abnormal findings in blood or urine



FIG 260 CALCINOSIS UNIVERSALIS IN A CHILD OF THREE Multiple nodules developed under the skin at the age of 1 occasionally requiring incision because of fluctuation. All calcium deposits were amorphous. Laboratory studies were normal. Urine calcium 97 mg/24 hrs. NPN 19 mg %. Serum calcium 9.4 and 10.0 mg %. Serum phosphorus 4.5 and 5.1 mg %. Serum alkaline phosphatase 4.5 U/L. Blood chlorides 98 mEq/L. Carbon dioxide combining power 24 mEq/L. No treatment known.



FIG 261 METASTATIC CALCINOSIS (See also Protocol 38 XVIII) The condition was associated with renal insufficiency and may have been caused or aggravated by excess vitamin D intake (see 38 XIV C 1). (Bottom) Note also marked arterial calcification (arrows) (Kaufman M and Dow J W. Hyperparathyroidism with calcinosis probably secondary to renal disease. *Lahey Clin Bull* 5:21-26).

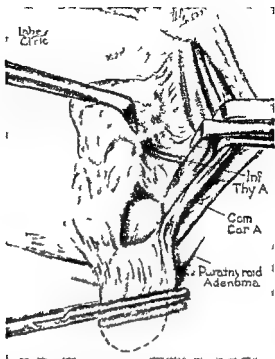
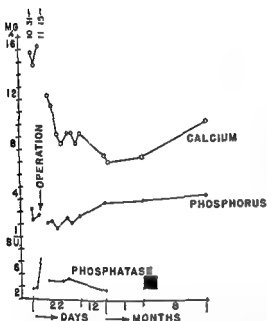


FIG 26/ PARATHYROID ADENOMA DESIDE COMMON CAROTID AND BELOW INTERIOR THYROID ARTERY (Lahey F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)

CHART 84 HYPERPARATHYROIDISM DUE TO PARATHYROID ADENOMA Chart showing changes in serum calcium and phosphorus after removal of parathyroid adenoma Dihydrotachysterol (AT 10) (solid black square) was used temporarily because of mild tetany No bone changes were noted in this patient Chief complaint was stiffness in anterior thigh and calf muscles Findings before and after operation are listed below

	BEFORE OPERATION	3 TO 4 WEEKS AFTER OPERATION
Urine specific gravity	1 009 1 008 1 007	1 010 1 015
RBC	4 400 000	3 500 000
Hgb	86%	76%
NPN	40 mg %	31 mg %
Total plasma protein	6 4 Gm %	9 0 Gm %
Albumin	4 4 Gm %	4 7 Gm %
Globulin	1 9 Gm %	4 3 Gm %
PSP	15% (1/2 hr)	25% (1/2 hr)
Urea clearance test	43%	53%

Some improvement in renal function within a month after operation

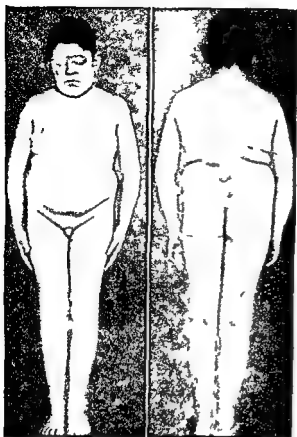


FIG 265 NEUROFIBROMATOSIS WITH TYPICAL CAFÉ AU LAIT PIGMENTATION (SMOOTH-EDGED) BONE CHANGES AND PITUITARY DWARFISM

Family history Mother and sister have similar pigmentation and evidence of neurofibromatosis

Past medical First abnormality observed was cryptorchidism for which an unsuccessful operation was performed at 16 years Retarded mental and physical development (IQ—59)

Physical examination Age 18 Weight 102 lbs Height 56 in Development as shown in photograph Two small subcutaneous nodes on either side of neck in occipital region Visual fields normal Testes not palpable

Roentgenographic findings Floor of sella depressed and posterior clinoids calcified Ventriculograms normal Bone age 11 years Lower end of left femur and upper end of right fibula show small areas of increased radiance and appear as cysts

Pathologic diagnosis Nodule—neurofibroma

Comment Roentgen findings and general physical status suggested craniopharyngioma however this could not be verified Neurofibromatosis with a neurofibromatous lesion adjacent to the sella could account for the whole picture

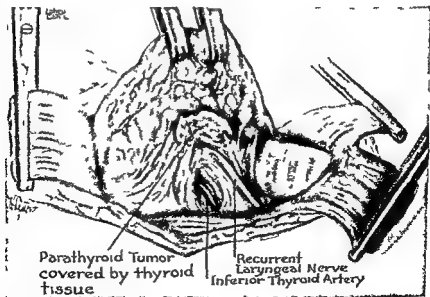


FIG 266 PARATHYROID ADENOMA DEEP BEHIND THYROID GLAND (Lahey F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)

CHAPTER 5

Adrenals (SUPRARENALS)

PRECLINICAL

Section 39 PRELIMINARY

- I HISTORY
- II ANATOMY
- III EMBRYOLOGY
- IV CONGENITAL ANOMALIES
- V HISTOLOGY
- VI FUNCTIONS
- VII CHEMISTRY
- VIII BIO ASSAY
- IX PATHOLOGY
- X CLASSIFICATIONS
- XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION
- XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION
- XIII EXAMINATION OF PATIENT

CLINICAL

Section

- 40 ADDISON'S DISEASE
 - 41 WATERHOUSE FRIDERICHSEN SYNDROME
 - 42 ADRENOGENITAL SYNDROME
 - 43 FEMINIZING SYNDROME DUE TO MALIGNANT ADRENAL CORTICAL TUMOR
 - 44 HYPERFUNCTION OF ADRENAL MEDULLARY OR OTHER CHROMAFFIN TISSUE DUE TO PHEOCHROMOCYTOMA
-

CHART 85 HYPERPARATHYROIDISM WITH RENAL INSUFFICIENCY PERSISTING AFTER CURE

Family history Negative

Past medical Negative

Chief complaint Pain in knees and legs

History of present illness On set 3 years previous after removal of stone from kidney

Physical examination Age 53 female married Weight 141 lbs Height 63 in BP 172/102 Dorsal round back Crepitation of knees

Laboratory data Urine albumin 2 plus sugar absent, specific gravity 1.008 alkali sediment 15 to 20 WBC Sulkowitch 1 plus PSP 15% excretion of dye RBC 3 490 000 Hgb 74% WBC 9 300 Blood NPN 63 mg % Serum calcium 14.4 mg % Serum phosphorus 3.6 mg % Serum alkaline phosphatase 46 B.U. Sedimentation rate 98 mm/hr

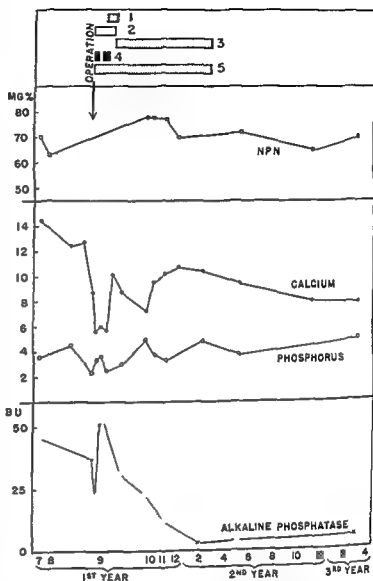
Röntgenographic findings Knees—decalcification with cystlike areas in lower femoral shaft Pelvis—marked osteitis fibrosa cystica Flat plate of abdomen—stones in left kidney

Treatment Removal of parathyroid adenoma 3½ cm in diameter Postoperative course—oliguria for several days No tetany with treatment

Progress BP 3 years after operation 128/100 Blood NPN 63 mg % Serum calcium 9.0 % Serum phosphorus 4.0 % Serum alkaline phosphatase 2.6 B.U.

Comment Taking calcium lactate and low protein salt free diet Doing well under care of a urologist

Symbols (1) A.T. 10—0.625 mg daily (2) Parathyroid extract—100 units daily (3) Vitamin D—50 000 units daily (4) Calcium gluconate—20 cc intravenously (5) Calcium lactate—180 gr daily



SECTION 39

PRELIMINARY

I HISTORY

1564	Eustachius ²³	First description of adrenals
1629	Jean Riolan ² (The Younger)	Suprarenal capsules ' was used for the adrenal glands
1651	Thomas Bartholinus Valsalva (1666 1723) ⁶⁶	Adrenals distinct from the kidneys, medulla recognized The adrenals were believed to be connected to the gonads by a duct
1756	Cook ¹⁸	A case of obesity excess hair and adrenal tumor was recorded (unverified)
1802	Bevan and Romkild ¹⁷	Child described who looked like a woman Adrenal tumor found on postmortem examination
1816	Otto ¹⁶	Hypertrophy of the adrenals found in hypergenitalism
1824	Combe ¹⁷	Condition now known as Addison's disease reported
1839	Bergmann ⁹	Relation of the adrenal medulla to the nervous system was recognized
1840	Gulliver ²⁰	Sphenoidal bodies identified within the adrenals
1846	Ecker ²²	Adrenal cells had a glandular function and secreted into the blood or lymphatics
1846	Goodsir ²⁸	Adrenals do not become distinct organs until testes ovaries and kidneys have appeared they retain the original texture of blastoderm
1849	Addison ³	First description of hypofunction of the adrenal glands
1856	Brown Séquard ¹⁴	Removal of adrenals was fatal in animals
1856	Vulpian ⁷⁰	Reaction for adrenaline in the adrenal glands
1865	de Crecchio ¹⁰	Adrenal hypertrophy described in a 40 year old female pseudohermaphrodite—an early case of adrenogenital syndrome probably initiated late in fetal life
1865	Henle ²²	Chromaffin reaction discovered and believed due to presence of adrenaline granules
1870	Heppner ²³	Hyperplasia of accessory adrenals located in broad ligaments and also normal adrenal glands were discovered in a 2 month old infant presumably male having a hypospadiac penis prostate and ovaries without any follicles
1882	Goodhart ⁷	Simple atrophy of suprarenal capsules first reported
1889	Thornton ⁶⁴	First successful removal of adrenal tumor associated with hirsutism and mammary regression
1892	Berdez ⁸	Original report of a medullary tumor
1894	Voelcker ⁶⁹	Primary description of fulminating purpura with bilateral adrenal hemorrhage
1895	Moore ⁴³	Sphenoidal bodies (later called chromaffin) were related to pressor substances
1895	Oliver and Schafer ⁴	Pressor substance (adrenalin) was found in the adrenal medulla
1896	Fraenkel ³	Active principle of medulla was recognized
1897	Abel ¹	Pressor substance called 'epinephrine'
1897	Neusser ⁴⁴	Medullary tumors are associated with hypertension
1901	Aldrich ³	Successful (independent of Takamine) isolation of crystalline adrenalin formula— $C_8H_{13}NO_3$ this was the first hormone to be isolated

1935	Whitehorn	Chemical method for estimating epinephrine in blood
1936	Truszkowski and Zwemer ¹⁴	Low potassium diet advised for Addison's disease
1937	Beer, King and Prinzmetal ⁷	First demonstration of adrenalinlike pressor substance in the blood during an attack of paroxysmal hypertension
1937	Britton and Silvette ¹⁵	Carbohydrate metabolism role of adrenals analyzed
1937	Steiger and Reichstem ⁸	Desoxycorticosterone synthesized
1937	Young ³	Genital and adrenal abnormalities summarized ✓
1938	Simpson ⁷	Synthetic desoxycorticosterone used for Addison's disease
1939	Ferrebee et al. ⁴	Desoxycorticosterone given by intramuscular injection for Addison's disease
1939	Thorn ⁶²	Treatment of Addison's disease with pellets of desoxycorticosterone
1940	Dijkhuizen and Behr ⁷⁰	Case of adrenal hyperplasia with Addison's disease and virilism reported
1944	Duncan Semans and Howard ¹	Pheochromocytoma with diabetes described, the latter was cured by removal of tumor
1945	Venning ⁶⁸	Demonstration of high urinary glycolytic steroids in pregnancy
1948	Hench and Kendall ³⁶	First injection of compound E in human for rheumatoid arthritis

II ANATOMY¹⁻⁴

A LOCATION AND DESCRIPTION

- 1 The two suprarenals are
 - a Situated on the upper pole of each kidney (11th to 12th thoracic to 1st lumbar vertebrae)
 - b Yellowish or brownish yellow bodies
 - c Surrounded by alveolar tissue containing fat
 - d Invested by a tough capsule through which pass numerous fibrous processes and vessels
- 2 Right adrenal
 - a Triangular shape bearing a resemblance to a cocked hat
 - b Relationships
 - (1) In contact with liver
 - (2) Behind inferior vena cava
 - (3) In front of diaphragm
 - c Peritoneal coverings
 - (1) Upper part of its lateral surface is devoid of peritoneum
 - (2) Inferior portion is covered by peritoneum reflected from the coronary ligament
- 3 Left adrenal
 - a Crescentic shape
 - b Relationships

- (1) Separated by peritoneum from cardiac end of stomach or spleen
- (2) In contact with pancreas and splenic artery
- c Peritoneal coverings
 - (1) Upper area of its anterior surface is lined by peritoneum of ommental bursa
 - (2) Lower area is devoid of peritoneum

B PARTS

- 1 External or cortex
 - a Color
 - (1) Externally—red or yellowish brown
 - (2) On section—yellow or orange
 - b Stratified
 - c Firm
 - d It forms the greater part of the gland (60 to 80% of total mass)
- 2 Internal or medulla
 - a Dark brown due to the presence of a very abundant blood supply
 - b Soft
 - c Pulpy

C WEIGHT^{3,4}

- 1 Considerable variations
 - a Average—6 to 8 Gm

1901	Little ³²	Adrenal apoplexy recognized
1901	Pepper ⁴⁷	A case with adrenal medullary tumor recorded
1901	Iakamine ⁶	Adrenalin isolated
1904	Stolz ⁶⁰	L-pinephrine synthesized
1905	Bulloch and Sequeira ¹	Adrenogenital syndrome identified ✓
1907	Hutchison ²	Suprarenal sarcoma in children was studied
1909	Porges ¹	Hypoglycemic attacks occur in Addison's disease
1910	Apert ⁴	Cases of adrenal hypertrophy (or 'hyperpinephric syndrome') summarized
1911	Stewart ⁹	Biologic tests for adrenalin in blood
1911	Waterhouse ⁷¹	All cases of adrenal hemorrhage and fulminating purpura were summarized
1914	Holmes and Sargent ³¹	Complete cure of a masculinized female due to benign adrenal tumor (first reported in 1924) Operation performed by Sargent
1915	Cannon ¹⁰	Theory of 'emergency function' of adrenals proposed
1916	Marshall and Davis ⁴¹	Nonprotein nitrogen increased in adrenalectomized animals
1918	Friderichsen ⁶	Second summary of cases with adrenal hemorrhage and fulminating purpura (Waterhouse Friderichsen syndrome)
1919	Bittorf ¹¹	Clinical picture of feminism in males may be due to adrenal neoplasm
1922	Labbe Tinel and Doumer ⁸	First clear description of paroxysmal hypertension caused by pheochromocytoma
1926	Roux	Successful removal of pheochromocytoma, but blood pressures were not recorded
1926	Vaquez and Donzelot ⁶⁷	Clinical diagnosis of pheochromocytoma
1927	Baumann and Kurland ⁶	Sodium decreased and potassium increased with adrenal insufficiency (blood)
1927	Hartman, MacArthur and Hartman ²¹	A substance (cortin) prolongs life of adrenalectomized cats
1927	Mayo ⁴	First successful exploration for cause of paroxysmal hypertension tumor removed with cure
1927	Rogoff and Stewart ⁴	A substance (interrenalin) increased the life span of adrenalectomized dogs
1928	Szent Gyorgyi ⁶¹	Cevitamic acid found in adrenal cortex
1929	Pliffner and Swingle ⁴⁹	Method of preparing extract of adrenal cortex (first 'potent extract')
1929	Pincoffs ⁴⁰ and Shipley ⁶	First preoperative diagnosis of chromaffin tumor as cause of paroxysmal hypertension
1929	Rogoff and Stewart ³	Adrenal cortical extract (interrenalin) used in the treatment of Addison's disease
1931	Perla and Gottesman ⁴⁸	Cortinlike properties of urine demonstrated
1932	Loeb ¹⁰	Adrenal control of electrolyte metabolism studied
1933	Broster and Vines ¹³	Cortical cells of adrenals in virilism showed an abnormal red color with Ponceau fuchsin stain
1933	Harrop et al ⁶	Sodium chloride restriction precipitated crises in Addison's disease
1934	Kendall et al ³⁷	Crystalline form of cortin isolated

by a formation of folds and a process of invagination which results in more intimate contact of the medulla and cortex

- 5 Sixteen (121 mm) Chromaffin manufactures epinephrine, but not until after birth

simultaneously with androgenic zone of adrenals during infancy

- b Hermaphroditism may develop
- c Later in life these may give rise to tumors which cause virilism in females
- d Pheochromocytoma

V HISTOLOGY (see Fig 268)^{1,2}

- 1 CORTEX (3 zones are recognized the λ zone is still questionable)

- 1 Zona glomerulosa
 - a Layer immediately beneath the capsule
 - b Cells are arranged in groups with a suggestion of alveolar structure
- 2 Zona fasciculata
 - a Is continuous with glomerulosa portion
 - b Consists of columns of cuboidal cells arranged radially
 - c Comprises the greatest part of cortex
 - d Is rich in lipid material
 - e Changes during life span
 - (1) Childhood—narrow edge of tissue
 - (2) Puberty
 - (a) Width composed of 2 or 3 cells
 - (b) Cellular columns are long
 - (c) Cells firmly packed
 - (3) Maturity
 - (a) Cellular columns are shorter
 - (b) Cells are packed less closely

- 3 Zona reticularis
 - a Innermost zone lying next to medulla
 - b Cells
 - (1) Irregular loose arrangement
 - (2) Abundant fine droplets of lipid
 - c Changes in lifetime
 - (1) After second decade it contains pigment
 - (2) With aging
 - (a) Zone widens
 - (b) More vascular
 - (3) Late in life may equal the fascicular zone in size

- 4 λ zone (see 39 IX C)
 - a At birth there is a large zone (λ) between the
 - (1) Zona reticularis
 - (2) Medulla

IV CONGENITAL ANOMALIES

A CORTICAL TISSUE

- 1 Aplasia³
- 2 Hypoplasia

B MALFORMATION⁴

- 1 One adrenal only
- 2 Both glands fused as one
- 3 Kidney and adrenal wholly or partially within the same capsule

C ACCESSORY AND ABERRANT TISSUE^{4,5}

- 1 Types
 - a Cortical tissue alone
 - b Cortical and medullary portions
 - c Medulla only (paraganglia)
- 2 Location
 - a Beneath the lower pole of kidney along spermatic artery
 - b Iliopsoas muscle
 - c Solar plexus
 - d Renal plexus
 - e Spleen
 - f Transverse colon
 - g Liver
 - h Pancreas
 - i Spermatic cord
 - j Epididymis
 - k Rete testis
 - l Ductus deferens
 - m Paradidymis
 - n Broad ligament³
 - o Fallopian tubes
 - p Ovaries
 - q Intercoastal spaces
 - r Arteries³
 - (1) Coronary
 - (2) Aorta
 - (3) Pulmonary

3 Outcome

- a Common at birth but disappear

- b Range—4 to 18 Gm
 c Left usually larger than right
 2 A single gland is present occasionally, or the two glands may be fused as one
 3 During life²
- | | PER CENT OF
BODY WEIGHT |
|----------------------|----------------------------|
| a Fourth fetal month | 0.46 |
| b Birth | 0.23 |
| c Adult | 0.01 |
- 4 Total volume is about 5 cc
 D SIZE (average, variable) ^{2 4}
- | | CM |
|-------------|-----|
| 1 Length | 4.5 |
| 2 Width | 3.3 |
| 3 Thickness | 0.5 |
- E BLOOD AND LYMPH SUPPLY
 1 Arteries
 a Derivation from the
 (1) Aorta
 (2) Inferior phrenic
 (3) Renal
 b Very rich separate blood supply to cortex and medulla about 6 to 7 cc /Gm of tissue/min⁵
 2 Veins
 a Near the anterior border of each gland there is a short furrow, the hilum from which the adrenal vein emerges
 b Right adrenal empties into the inferior vena cava
 c Left adrenal
 (1) Empties into the renal vein
 (2) May open directly into inferior vena cava
 d Cortex has no marked venous system
 3 Lymphatics
 a All drain into lumbar glands
 b Cortical—pass through the connective tissue septa with the blood vessels
 c Medullary—accompany the larger venules and form a plexus around central vein
 F NERVES
 1 Numerous fibers form suprarenal plexus
 2 Fibers from
 a Greater splanchnic (chief supply)
 b Renal plexus
 c Celiac
 (1) Plexus
 (2) Ganglion
 d Vagus (questionable)

- e Phrenic
 f Lumbar sympathetic ganglia
 3 Nonmyelinated type within gland
 4 Medulla
 a Richer supply than cortex
 b Small ganglia and single neurons within parenchyma

III EMBRYOLOGY^{1, 3}

- A CORTEX (origin from splanchnic mesoderm)
 1 Four weeks (6 mm) There is a proliferation of epithelial cells which lie between the mesonephros and the root of mesentery
 2 Six weeks (12 mm) The buds of tissue thus formed lie as a continuation of the suprarenal ridge
 3 Birth Almost the entire gland is composed of cortical tissue
 B MEDULLA (ectodermal origin, development according to weeks)
 1 Three (9 mm) Ganglionated cord and sympathetic nerve plexus
 2 Six (16 mm) Visceral ganglia, cells give rise to chromophil tissue sympathochromophil tissue formed
 3 Seven to 8 (20 mm) The sympathochromophil cells begin to migrate into the developing cortex along the central vein to form the medulla differentiation of the chromophil cells begins but is not complete until birth
 4 After 8 Penetration of the epithelial anlage is accompanied

(f) Other functions may be conjectured on basis of the

[1] Changes occurring in abnormal states

[2] Role assigned to actions of known or supposed hormonal groups

(6) In the female, it influences or may be entirely responsible for sexual and body hair independent of its protein anabolic or androgenic influence

(7) It contributes to reproductive capacity, although this may be purely a secondary effect

(8) The following list of actions have also been postulated

(a) Lipoid (lipocorticoids) — stimulation of fat metabolism

(b) Trichogenic — sexual hair growth

(c) Antipigmentation

(d) Reproductive [N' (?) hormone²]

(e) Bone maturation

(f) Estrogenic

(g) Renal

(h) Mammogenic

(i) Lactogenic⁷

4 Medulla

a General

(1) Not essential to life²

(2) Cardiovascular dynamics influenced

(3) Minor regulator of electrolytic balance

b Epinephrine may cause stimulation and release of pituitary adrenocorticotropin which is important in times of acute stress to protect the organism immediately and latently

(1) Acute stage through action of epinephrine or nor epinephrine upon the tissues (liver blood vessels, etc)

(2) Chronic stage of resistance by the adrenocortical hormones

c Nor epinephrine

(1) Certain functions which are antagonistic to epinephrine

(2) No effect on adrenocorticotropin of pituitary⁸

B INDIVIDUAL HORMONES

1 Cortical hormones

a Introduction

(1) It is fairly certain that these are under pituitary control

(2) Current opinion leans toward the hypothesis that only one pituitary adrenocorticotrophic hormone (ACTH) maintains the secretion of all adrenocortical hormones (see 2 VI B 6)

(3) The number or exact nature of of the hormones of the adrenal cortex is still unknown

(4) The cortex appears to influence many metabolic processes although our knowledge to date is still fragmentary

(5) Certain general actions are indicated by laboratory and clinical observations

(6) List of the possible hormones and their current terms

(a) Carbohydrate — sugar or S' glucocorticoids or anti anabolic hormones (Compounds A B E F)

(b) Protein anabolic—nitrogen retaining or N, testoids or androgenic hormone (androsterone)

(c) Electrolytic — sodium potassium or water metabolic hormones or mineral corticoids (desoxycorticosterone) (see Table 47)

(d) Miscellaneous and hypothetical hormones which may or may not have been included

b 11 dehydrocorticosterone (compound A of Kendall) and 17 hydroxy 11 dehydrocorticosterone (compound E of Kendall)

(1) Animals (effect on intact rats using about 5 mg / 24 hrs)

(a) Inability to use carbohydrate resulting in diabetes —insulin resistant²⁸

(b) Pancreatic diabetes intensified³⁴

(c) Gluconeogenesis varies³⁵

- b This "fetal zone" undergoes involution during first year of life
- c Significance is still a matter of controversy

II MEDULLA

- 1 Chromophil (chromaffin) cells
 - a Are scattered irregularly without any semblance of order
 - b Vary from cylindrical to irregular, polyhedral forms
- 2 Very vascular tissue
- 3 Sinusoids are interspersed throughout the intercellular meshes allowing intimate contact between the cells and the blood stream
- 4 Contents
 - a Nonmedullated nerve fibers in great abundance
 - b Sympathetic ganglia are found occasionally

VI FUNCTIONS

A GLAND AS A WHOLE

- 1 Although derived from entirely different embryologic tissue, the cortex and medulla are a unit anatomically
- 2 The cortex is under the control of the anterior pituitary, whereas the medulla apparently is not (see 2 VI B 9)
 - a The trend of evidence favors one adrenocorticotrophic hormone as regulating all adrenocortical functions
 - b The exact interrelationships or interdependence have not been fully determined
- 3 Cortex³
 - a Essential for existence, but precisely upon which functions or hormones life is absolutely dependent is still unknown
 - b Its functions must be numerous, many of which have yet to be discovered and even those known need more verification
 - (1) Carbohydrate metabolism is influenced in the manner that can only be inferred from the abnormal disturbances observed in adrenocortical syndromes and following injection of certain adrenocortical compounds or adrenocorticotropin^{2 6}
 - (a) Some steroids may be held

within the adrenal gland to aid in the daily metabolic processes or for use under stress

- (b) Liver glycogen storage facilitated
 - (c) Sugar conservation by the tissues
 - (d) Protein conversion into sugar
 - (e) Defense mechanism
- (2) Evidence points to a role in immunity through the
 - (a) Release of gamma globulins
 - (b) Genesis of phagocytic cells
 - (3) Part played possibly by increased activity in
 - (a) Anoxia
 - (b) Abnormal internal or environmental temperatures
 - (c) Various intoxications as food or chemical poisoning
 - (4) A large group of damaging agents, including
 - [1] Surgical operations
 - [2] Anesthesia
 - [3] Injury
 - [4] Burns
 - [5] Congestive heart failure
 - (4) Bodily growth process is aided through anabolic effects⁴
 - (5) Control or sustenance of electrolytic balance is undoubtedly a continuous necessity
 - (a) One of the most important and vital functions
 - (b) Action on the renal tubules and sweat glands by promoting
 - [1] Sodium chloride retention
 - [2] Potassium excretion
 - (c) Blood pressure maintained
 - (d) Chief regulator of these leaving the medulla to act in emergencies
 - (e) Hyperactivity tends to preserve loss of electrolytes from excessive sweating and this accounts for acclimatization to high external temperatures

- (b) Hypoglycemia—retarded
- (c) Conversion of protein and fat to carbohydrate enhanced
- (d) Blood pressure—elevated
- (e) Sodium—conserved
- (2) Adrenalectomized animals (see 39 VI C)
 - (a) Large doses are not toxic
 - (b) Animals maintained in perfect health
- e Desoxycorticosterone (animals and humans) ^{1 23 37 9 11 17 5 60}
 - (1) General health—improved
 - (2) Weight—increased by prevention of fat depletion^{7 10}
 - (3) Blood pressure—elevated (more so in adrenal insufficiency; this may not be due to an increase in plasma volume)
 - (4) Carbohydrate metabolism—may be altered¹⁰
 - (5) Phosphatase content of bones—increased¹⁰
 - (6) Urinary excretion—increased^{20 23, 60 61}
 - (a) Output
 - (b) Potassium
 - (7) Potassium (serum)—lowered if high^{4 10}
 - (8) Sodium and chloride (blood)—increased if low^{23, 38 39}
 - (9) Plasma volume—increased^{30 31}
 - (10) Toxic in excessive doses causing (see 40 VI D)¹³
 - (a) Sodium retention in excess
 - (b) Hypertension
 - (c) Cardiac enlargement
 - (d) Edema
 - (e) Tendon contractures¹⁴
- f Amorphous fraction¹²
 - (1) Devoid of carbohydrate effects
 - (2) Action largely on electrolytes
- (3) More potent than synthetic desoxycorticosterone
- (4) Rate of growth—may increase⁴³
- (5) Phosphatase content of bones—unchanged¹⁰
- g Fat factor—deposition of fat may be regulated by the adrenal cortex^{31 47}
- 2 Medullary hormones
 - a. Epinephrine⁴³
 - (1) Vascular changes^{10 23 34 41 44}
 - (a) Peripheral resistance decreased
 - (b) Heart rate increased, then decreased
 - (c) Amplitude of heart beat and output increased
 - (d) Coronary vessels dilated in experimental animals³
 - (e) Systolic blood pressure only raised, later drops
 - (f) Pressor effect reversed by ergotamine
 - (2) Hyperglycemic action (see 103 I H 4)^{9 14 15 17}
 - (a) Effect dependent on amount of liver glycogen
 - (b) Liver glycogen may be raised, after a serious depletion by formation of lactic acid (Cori cycle)
 - (c) Muscle glycogen changed into lactic acid for conversion to liver glycogen
 - (3) The following are increased
 - (a) Fat oxidation¹⁴
 - (b) Protein catabolism^{18 33}
 - (c) Heat production⁶
 - (d) Oxygen consumption¹
 - (e) Carbon dioxide formation¹⁷
 - (f) Lactate output⁷
 - (4) Variable effects on the following depending on dosage and species
 - (a) Skin and mucous membranes¹¹

TABLE 47. ACTION OF VARIOUS STEROIDS ON SODIUM AND POTASSIUM EXCRETION¹³

STEROID	HORMONELIKE ACTION	SODIUM	POTASSIUM
Desoxycorticosterone (DOC A) (synthetic)	Salt	Decreased	Increased
17 hydroxycorticosterone (isolated from adrenal cortex)	Carbohydrate metabolism	Increased	Increased
Testosterone (synthetic)	Androgenic nitrogen retaining	Decreased	Decreased

- (d) Glycogen deposited in liver of adrenalectomized mice⁷
8 4⁷ 2³
- (e) Weight⁴⁴
 - [1] Loss with compound E
 - [2] Gain with compound A
- (f) Increased urinary output of⁹
 - [1] Water
 - [2] Nitrogen
 - [3] Potassium
 - [4] Phosphorus (inorganic)
 - [5] Chlorides
 - [6] Ketones
- (g) Sodium retention
- (h) Growth inhibited⁴² or sustained in adrenalectomized animals³⁶ 84
- (i) Focal necroses in skeletal and cardiac muscles with calcification (mice)⁴⁸
- (j) Kidney size—increased⁴⁷
- (k) Resistance to stress increased³³ 4
- (l) Lymphoid tissue lysis
- (m) Circulating eosinophils and lymphocytes decreased
- (n) Life maintained in adrenalectomized animals⁸ 88
- (o) Phosphatase content of bones is decreased⁸⁸
- (2) Humans with Addison's disease treated with compound A⁶⁹ 7
 - (a) Urinary excretion⁹
 - [1] Decreased
 - [a] Sodium
 - [b] Chloride
 - [2] Increased
 - [a] Water (may be decreased)
 - [b] Nitrogen (questionable)
 - [c] Potassium
 - [d] Phosphorus (not consistent)
 - (b) It does not replace desoxy corticosterone (DOCA)
 - (c) Equivalent to adrenocortical extracts
- (3) Effect on humans with compound E
 - (a) Changes listed under effects on animals (found in part at least)
 - (b) Addison's disease
 - [1] Electrolytic balance maintained⁶
 - [2] No consistent changes in⁶⁰
 - [a] Phosphorus (urinary)
 - [b] Protein (serum)
 - [c] A/G ratio
 - [d] Blood lipoids
 - [e] 17 ketosteroids
 - [3] Increased urinary excretion of⁶⁰
 - [a] Sodium chloride (transient)
 - [b] Cortinlike substances
 - (c) Sodium excretion may be increased when there is over treatment with desoxycorticosterone (DOCA)⁸
 - (d) Diabetes may be intensified³
 - (e) If anemia exists, there may be an increase in
 - [1] Red blood cells
 - [2] Hemoglobin
 - (f) Alpha waves of electro encephalogram increase in frequency⁵
 - (g) For therapeutic and toxic effects see 107 VIII F 1, M 2 a
- c 17 hydroxycorticosterone (compound F of Kendall) (effect in rats or normal or adrenal insufficient humans using 20 mg / 24 hrs)⁹ 79
 - (1) Urine—increased output (variable) of
 - (a) Nitrogen
 - (b) Sodium
 - (c) Potassium
 - (d) Phosphorus (inorganic)
 - (e) Chlorides
 - (2) Circulating eosinophils and lymphocytes—decreased
 - (3) Sugar (blood)—increased⁴⁹
 - (4) Uric acid (serum)—increased
 - (5) Phosphorus (inorganic, serum)—lowered
 - (6) Resistance to stress—increased³
- d Adrenal cortical extracts (commercial) in
 - (1) Adrenal insufficiency (human)
 - (a) Liver glycogen—increased

C ADRENALECTOMY (see Chart 86)^{22 31}

1 There is a gradual development of the following

- a Anorexia
- b Vomiting
- c Bloody diarrhea
- d Profound muscular weakness probably due to¹
 - (1) Large amounts of sodium
 - (2) Less than normal potassium

e Salivation

f Restlessness

g Clonic movements

h Stupor

i Convulsions

j Cessation of lactation

k Anuria^{9 10 13 14}

2 Miscellaneous effects

a No change in growth rate (rats)⁴³

b Decrease in

- (1) Body temperature^{16 34}
- (2) Basal metabolic rate
- (3) Blood pressure
- (4) Blood volume⁴³
- (5) Rate of blood flow^{9 13 14}
- (6) Polymorphonuclears¹³
- (7) Sugar (blood) (see Table 101)
 - (a) Normal at times
 - (b) Level depends on duration of abstinence from food^{30 4}

(8) Sodium (serum)

(9) Chlorides (serum)

(10) Carbon dioxide capacity

(11) Bicarbonate

(12) Glutathione

(13) 17 ketosteroids — excretion of 2 mg/24 hrs persists in males who have been castrated and adrenalectomized for carcinoma of prostate thus pointing to an other source of their formation¹

c Increase in

- (1) Erythrocytes¹⁷
- (2) Hemoglobin
- (3) Lymphocytes⁴⁴
- (4) Hematocrit
- (5) Capillary permeability^{8 36 39}
- (6) Nonprotein nitrogen
- (7) Urea¹⁷
- (8) Protein (may be decreased)^{17 19}
- (9) Potassium⁴

(10) Calcium³

(11) Phosphorus

(12) Magnesium

(13) Oxygen capacity of blood^{6 10 13 14}3 Reaction to stress toxins chemical agents is increased¹⁹

4 Pathologic physiology

a Increased capillary permeability is assigned as the cause of blood plasma loss and the redistribution of water throughout the body

(1) Body cells absorb water from interstitial spaces

(2) Erythrocytes take water from plasma

b Renal excretion^{12, 21}

(1) Decreased

(a) Nitrogen

(b) Potassium which is released by body cells resulting in an elevated plasma level

(c) Ammonia

(2) Increased

(a) Water

(b) Sodium producing decrease in plasma concentration

(c) Chloride

(d) Bicarbonate

c Absorption of sugar from gastrointestinal tract is thought to be reduced (humans) but this has not been definitely proven^{4 35-37}

(1) Liver glycogen is not produced from glucose or is retarded

(2) Blood sugar is decreased

(3) Sugar is burned for energy purposes rather than converted into

(a) Protein

(b) Fat

(4) No abnormality occurs in animals if fed and maintained with salt

(5) Small intestinal reabsorption is markedly retarded for^{6 40}

(a) Sodium

(b) Potassium

(c) Chloride

d Reaction to stress and other similar episodes is due to an alteration in adrenocortical lymphoid tissue relationship

- (d) Glycogen deposited in liver of adrenalectomized mice^{7 8 46 52}
- (e) Weight⁴⁴
 - [1] Loss with compound E
 - [2] Gain with compound A
- (f) Increased urinary output of⁹
 - [1] Water
 - [2] Nitrogen
 - [3] Potassium
 - [4] Phosphorus (inorganic)
 - [5] Chlorides
 - [6] Ketones
- (g) Sodium retention
- (h) Growth inhibited^{2 43} or sustained in adrenalectomized animals^{30 31}
- (i) Focal necroses in skeletal and cardiac muscles with calcification (mice)⁴⁸
- (j) Kidney size—increased⁴⁷
- (k) Resistance to stress increased^{3 4}
- (l) Lymphoid tissue lysis
- (m) Circulating eosinophils and lymphocytes decreased
- (n) Life maintained in adrenalectomized animals^{8 86}
- (o) Phosphatase content of bones decreased⁸⁵
- (2) Humans with Addison's disease treated with compound A—^{69 75}
 - (a) Urinary excretion⁹
 - [1] Decreased
 - [a] Sodium
 - [b] Chloride
 - [2] Increased
 - [a] Water (may be decreased)
 - [b] Nitrogen (questionable)
 - [c] Potassium
 - [d] Phosphorus (not consistent)
 - (b) It does not replace desoxy corticosterone (DOCA)
 - (c) Equivalent to adrenocortical extracts
- (3) Effect on humans with compound E
 - (a) Changes listed under effects on animals (found in part at least)
- (b) Addison's disease
 - [1] Electrolytic balance maintained⁷⁸
 - [2] No consistent changes in⁶⁹
 - [a] Phosphorus (urinary)
 - [b] Protein (serum)
 - [c] A/G ratio
 - [d] Blood lipoids
 - [e] 17 ketosteroids
 - [3] Increased urinary excretion of⁶⁹
 - [a] Sodium chloride (transient)
 - [b] Cortinlike substances
- (c) Sodium excretion may be increased when there is over treatment with desoxycorticosterone (DOCA)⁸
- (d) Diabetes may be intensified³
- (e) If anemia exists, there may be an increase in
 - [1] Red blood cells
 - [2] Hemoglobin
- (f) Alpha waves of electroencephalogram increase in frequency³
- (g) For therapeutic and toxic effects see 107 VIII F 1, VI 2 a
- c 17 hydroxycorticosterone (compound F of Kendall) (effect in rats or normal or adrenal insufficient humans using 20 mg / 24 hrs)^{30 70}
 - (1) Urine—increased output (variable) of
 - (a) Nitrogen
 - (b) Sodium
 - (c) Potassium
 - (d) Phosphorus (inorganic)
 - (e) Chlorides
 - (2) Circulating eosinophils and lymphocytes—decreased
 - (3) Sugar (blood)—increased⁴⁹
 - (4) Uric acid (serum)—increased
 - (5) Phosphorus (inorganic serum)—lowered
 - (6) Resistance to stress—increased³³
- d Adrenal cortical extracts (commercial) in
 - (1) Adrenal insufficiency (human)
 - (a) Liver glycogen—increased

- (b) Chromophilic reaction
- (2) Golgi apparatus changes during
 - (a) Inactivity—compact
 - (b) Activity
 - [1] Diffuse
 - [2] Ramifying
- (3) Ascorbic acid concentration
- (4) Lipids and ketosteroids
 - (a) Distributed in zona
 - [1] Glomerulosa
 - [2] Fasciculata, outer part
 - (b) Content as revealed by
 - [1] Sudan dye reaction
 - [2] Phenylhydrazine
 - [3] Schiff reagent
 - [4] Ammoniated silver nitrate
 - [5] Birefringence
 - [6] Acetone solubility
 - [7] Autofluorescence

b Summary

- (1) Zona glomerulosa may exist independent of the pituitary but certain sudanophilic material requires adrenocorticotropin
- (2) Zona fasciculata is entirely regulated by adrenocorticotropin
- (3) λ zone may possibly be controlled by LH

F ACTIVITY AT DIFFERENT PERIODS IN LIFE

1 Birth

a Size of adrenals

- (1) Large about one third that of a kidney, possibly because of stimulation by maternal and placental hormones
- (2) Rapid involution of cortex just after birth³

b Some writers have suggested that relative adrenal insufficiency may occur at this time^{3, 7}

c Urinary glyco-genic hormones are absent³

- 2 Three months of age—adrenals are reduced one half their size at birth
- 3 Childhood—cortical (mineral) and glyco-genic (S) hormones reach adult levels
- 4 Pubescence and puberty—effective secretion of certain cortical hormones cause
 - a Hair growth
 - b Bone maturation possibly

5 Adult

a Adrenal (each)

- (1) Weight—about 8 to 10 Gm
- (2) Size—approximately $\frac{1}{2}$ the size of a kidney

b Variations in histology and function according to the influences to which the adrenal gland is reactive

6 Pregnancy, lactation and menstruation

- a Some cortical enlargement is likely³
- b Cortical function—may be increased
- c Urinary glyco-genic hormones—increased⁶

7 Old age

- a Some shrinking of the glands probably giving rise to the hypothetical 'adrenopause'
- b Urinary 17 ketosteroids decline slightly, aside from those derived from the testes¹

G MISCELLANEOUS FACTORS INFLUENCING ADRENAL CORTICES (experimental and human)

1 Cortical enlargement (possibly) produced by³

- a Menstruation
- b Pregnancy
- c Lactation
- d Administration of
 - (1) Vitamin C
 - (2) Vitamin B
- e Undernutrition
- f High protein diet¹

2 Avitaminosis (guinea pig) may cause hemorrhagic changes in adrenals

3 Denervation of adrenal does not affect the cortex

4 Hibernation produces complete atrophy of both glands³

5 Cortical steroid and medullary chromaffin granules disappear during stress as with (see 99)³

- a Burns
- b Cold
- c Muscular exertion
- d Anesthesia
- e Trauma
- f Hemorrhage
- g Chemical agents
- h Poisons
 - i Acute infections
 - j Damaging factors

- (b) Salivary glands¹
- (c) Muscles^{11 0}
 - [1] Bronchioles
 - [2] Intestine³
 - [3] Gallbladder¹⁰
 - [4] Bladder³
 - [5] Male genital organs
 - [6] Uterus (contraction in pregnant cat, relaxation in nonpregnant)¹⁰
- (d) Kidneys¹³
 - [1] Afferent arterioles—constricted
 - [2] Renal flow—decreased
 - [3] Output—reduced without affecting glomerular filtration
- (e) Circulating erythrocytes and leukocytes by^{3 3 0 6}
 - [1] Splenic contraction (variable)
 - [2] Bone marrow stimulation
- (f) Coagulation time³¹
- (g) Potassium (plasma)^{1* 17 4}
- (h) Blood volume¹⁰
- (5) Adrenocorticotropin effects may be enhanced⁶⁸
 - (a) Increase in urinary excretion of uric acid
 - (b) Decrease in
 - [1] Eosinophils
 - [2] Basophils
 - (c) 17 ketosteroids and 11 oxy steroids are not altered
- (6) Summary — sympathomimetic hormone
 - (a) Action on effector cells
 - (b) Sympathetic nervous system imitated
- b Nor epinephrine
 - (1) Vascular changes^{*}
 - (a) Peripheral resistance increased
 - (b) Heart rate
 - [1] Unchanged
 - [2] Slowed
 - (c) Cardiac output—not altered
 - (d) Diastolic as well as systolic blood pressure raised
 - (e) Pressor effect not reversed by ergotamine
 - (2) Hyperglycemic action — one eighth as effective as epinephrine¹
 - (3) Adrenocorticotrophic effect — no decrease in circulating eosinophils⁶
 - (4) Uterine muscle (nonpregnant cat)—not conspicuously relaxed⁴
 - (5) Oxygen consumption—increased³
 - (6) Lethal dose—one third as toxic as epinephrine³
- c Combined action of epinephrine and nor epinephrine³
 - (1) Vascular changes
 - (a) Mean arterial pressure falls slightly
 - (b) Cardiac output increased
 - (c) Peripheral resistance falls from levels produced by nor epinephrine alone
 - (2) Interpretation—vasoconstrictor action of nor epinephrine is blocked by epinephrine³
- d Comparison in normal and hypertensive persons—see Table 48

TABLE 48 COMPARISON OF EPINEPHRINE AND NOR EPINEPHRINE INFUSION IN NORMAL AND HYPERTENSIVE PERSONS IN APPROPRIATE DOSAGE³

	EPINEPHRINE	NOR EPINEPHRINE
Normal	Less sensitive to compound Vasodilation Cardiac stimulation Greater vasodilation than normal	More sensitive to compound Vasoconstriction No cardiac stimulation Greater vasoconstriction than normal (decreased epinephrine suggested as cause due to failure of methylation of nor epinephrine)
Hypertensive	Response similar to nor epinephrine induced hypertension in normals	

- (b) Chromophilic reaction
- (2) Golgi apparatus changes during
 - (a) Inactivity—compact
 - (b) Activity
 - [1] Diffuse
 - [2] Ramifying
- (3) Ascorbic acid concentration
- (4) Lipids and ketosteroids
 - (a) Distributed in zona
 - [1] Glomerulosa
 - [2] Fasciculata outer part
 - (b) Content as revealed by
 - [1] Sudan dye reaction
 - [2] Phenylhydrazine
 - [3] Schiff reagent
 - [4] Ammoniated silver nitrate
 - [5] Birefringence
 - [6] Acetone solubility
 - [7] Autofluorescence

b Summary

- (1) Zona glomerulosa may exist in dependent of the pituitary but certain sudanophilic material requires adrenocorticotropin
- (2) Zona fasciculata is entirely regulated by adrenocorticotropin
- (3) X zone may possibly be controlled by LH

F ACTIVITY AT DIFFERENT PERIODS IN LIFE

1 Birth

a Size of adrenals

- (1) Large about one third that of a kidney possibly because of stimulation by maternal and placental hormones
- (2) Rapid involution of cortex just after birth¹

b Some writers have suggested that relative adrenal insufficiency may occur at this time^{2, 7}

c Urinary glycolytic hormones are absent⁸

2 Three months of age—adrenals are reduced one half their size at birth

3 Childhood—cortical (mineral) and glycolytic (S) hormones reach adult levels²

4 Pubescence and puberty—effective secretion of certain cortical hormones cause

a Hair growth

b Bone maturation possibly

5 Adult

a Adrenal (each)

- (1) Weight—about 8 to 10 Gm
- (2) Size—approximately $\frac{1}{8}$ the size of a kidney

b Variations in histology and function according to the influences to which the adrenal gland is reactive

6 Pregnancy, lactation and menstruation

- a Some cortical enlargement is likely⁹
- b Cortical function—may be increased
- c Urinary glycolytic hormones—increased⁶

7 Old age

- a Some shrinking of the glands probably giving rise to the hypothetical adrenopause
- b Urinary 17 ketosteroids decline slightly aside from those derived from the testes¹

G MISCELLANEOUS FACTORS INFLUENCING ADRENAL CORTICES (experimental and human)

1 Cortical enlargement (possibly) produced by³

- a Menstruation
- b Pregnancy
- c Lactation
- d Administration of
 - (1) Vitamin C
 - (2) Vitamin B
- e Undernutrition
- f High protein diet¹

2 Avitaminosis (guinea pig) may cause hemorrhagic changes in adrenals

3 Denervation of adrenal does not affect the cortex

4 Hibernation produces complete atrophy of both glands²

5 Cortical steroid and medullary chromaffin granules disappear during stress as with (see 99)²

- a Burns
- b Cold
- c Muscular exertion
- d Anesthesia
- e Trauma
- f Hemorrhage
- g Chemical agents
- h Poisons
 - 1 Acute infections
 - 2 Damaging factors

- Fat metabolism is impaired
- f Elevation of nonprotein nitrogen is partially due to late impairment of renal function
- Amino acids
 - (1) Deamination decreased
 - (2) Used for energy purposes probably
- h Retardation of growth in animals may be related to loss of cortical androgenic influence plus other altered metabolic processes mentioned above which might discourage tissue synthesis¹⁻⁷ (Immature adrenalectomized rats or dogs live and grow on high sodium chloride, low potassium diet²²)
- i Gastric changes, as ulceration, are caused by a functional derangement in
 - (1) Motility
 - (2) Achlorhydria
- j Lactation prevented¹
- k Other findings are not explained so readily

5 Removal of medulla only is not followed by obvious insufficiency³⁹

- a Extra adrenal sources of epinephrine may be explanation
- b Loss detectable in emergencies
- 6 Effect on other endocrine glands
 - a Cortical hyposecretion or absence
 - (1) Pituitary—see 2 I \ II 16
 - (2) Thyroid—no significant alterations, possibly increased activity, then decreased⁴⁻²⁷
 - (3) Parathyroids—variable reports on serum calcium level¹⁻⁴³
 - (4) Testes or ovaries may become atrophic²⁸⁻³⁶
 - (5) Pancreas may show³
 - (a) Congestion
 - (b) Hemorrhage
 - b Medullary hyposecretion or absence retards adrenocorticotropin secretion

D HYPERHORMONAL EFFECTS

- 1 On various organs and functions
 - a Cortical hormones summarized under
 - (1) Individual hormones—see 39 VI B 1
 - (2) Cushing's syndrome
 - (3) Adrenogenital syndromes

- (4) Diabetes mellitus
- (5) Steroid metabolism

b Medullary hormones summarized under

- (1) Individual hormones—see 39 VI B 2

(2) Pheochromocytoma

2 On other endocrine glands

a Cortical hormones

- (1) Pituitary—see 2 I \ II 17, 11 A B 1

- (2) Thyroid—may depress function through pituitary¹⁻⁴⁻⁶⁻⁷

- (3) Parathyroids—serum calcium may decrease¹⁰

- (4) Gonads—"S" hormones may inhibit function

- (5) Pancreatic islands—"S" hormones may inhibit insulin production or effectiveness

b Medullary hormones

- (1) Insulin production or effectiveness may be inhibited³⁻⁸

- (2) Thyroid³⁻⁹

- (a) Iodine may be released
- (b) Hyperplasia (possible)

E HISTOPHYSIOLOGY

1 Origin of secretions

a Cortical hormones

- (1) Zona glomerulosa is believed to elaborate steroids (desoxycorticosterone) which influence salt and water metabolism (see below)⁴⁻⁶⁻⁶

- (2) Zona fasciculata produces the carbohydrate (11 oxycorticosteroids, "S" or sugar) hormones (see below)¹⁻⁶

- (3) Zona reticularis is considered by some to show hyperplasia and eosinophilia in the adrenogenital syndrome and therefore the source of the nitrogen (N) retaining hormone⁵

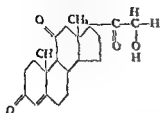
- b Medullary hormones (epinephrine)—see 44 \ B

2 Adrenal cortices³⁻⁸

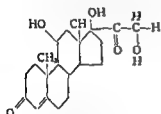
a Cortical activity is related to

- (1) Mitochondria (index of cell viability i.e., irregular size and poor staining may show that the cell is dying) by their
 - (a) Form

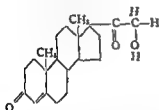
- 11 dehydrocorticosterone (compound A—Kendall)



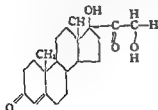
- d 17 hydroxycorticosterone (compound F—Kendall, V—Reichstein)



- e 11 desoxycorticosterone (compound Q—Reichstein, DOCA, DCA)



- f 17 hydroxy 11 desoxycorticosterone (compound S—Reichstein)



3 Properties

a Desiccated suprarenal¹⁴

- (1) Form—amorphous powder
- (2) Color—yellow to brown
- (3) Odor—characteristic
- (4) Solubility—partially in water

b Desoxycorticosterone¹

- (1) Form—crystalline powder
- (2) Color—white
- (3) Odor—none
- (4) Solubility

(a) Slight in vegetable oils

(b) Not in water

c Cortisone and hydrocortone

- (1) Form—crystalline powder
- (2) Color—white
- (3) Solubility—slight in water

II ADRENAL MEDULLARY HORMONES

I Nature

a Introduction

- (1) Epinephrine was first isolated from the adrenals and later synthesized^{20 1}
- (2) Nor epinephrine was first synthesized and later isolated from^{17 19}

(4) Cattle

- [1] Adrenergic postganglionic nerves^{2, 4, 1}
- [2] Adrenal medullary extracts³

(b) Man—pheochromocytoma⁵

(3) Both are amines

- (a) Epinephrine contains a methyl group, nor epinephrine does not
- (b) Epinephrine may be methylated in the body from nor epinephrine⁴

(4) Both are sympathetic mediators^{4 23}

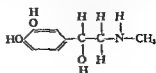
- (a) Epinephrine—vasodilator
- (b) Nor epinephrine—vasoconstrictor

b Commercial preparations

- (1) Epinephrine or adrenalin chloride (synthetic, levo)
- (2) USP epinephrine (adrenal extract not sold commercially) contains³
 - (a) Epinephrine from 0 to 36 per cent
 - (b) Nor epinephrine from 64 to 100 per cent

2 Formulas

- a Epinephrine (1 hydroxy 1 (3', 4 dihydroxyphenyl) 2 methylamino ethane adrenalin, suprenine, levo)



VII CHEMISTRY

A ADRENOCORTICAL HORMONES (or derived compounds)

1 Nature

a Introduction

- (1) Extracts of the adrenal cortex contain compounds which produce various actions, but their full interrelationships have yet to be established⁸
- (2) The likelihood of more than one cortical hormone has been questioned, but the divergent clinical syndromes due to adrenal pathology favor the existence of multiple hormones
- (3) Twenty eight or more steroid compounds have been isolated from animal adrenal glands, but few of these have been recovered from human urine¹¹
- (4) Some of the steroids derived from the adrenal cortex are physiologically active in different degrees
- (5) While it is desirable to separate the various actions of the compounds, it is probable that there is considerable overlapping of effects¹⁰
- (6) Pituitary adrenocorticotrophic hormone when injected in normal humans produces characteristic changes of the three main groups of adrenal hormones—(1) to (3) below

b Groups of adrenal steroids

- (1) Carbohydrate action (S, sugar, glucoid or antianabolic hormones characterized by oxygen on eleventh carbon atom)
 - (a) Corticosterone
 - (b) 17 hydroxy 11 dehydrocorticosterone (synthesized)
 - (c) 11 dehydrocorticosterone (synthesized)
 - (d) 17 hydroxycorticosterone
- (2) Androgenic action (all rather feeble—"N," nitrogen protein anabolic or testoid hormone)
 - (a) Adrenosterone
 - (b) Androsterone

~(c) Dihydroandrosterone (11 hydroxyisoandrosterone)

(d) 17 hydroxyprogesterone

(3) Electrolytic action (salt, water and potassium hormones)

(a) 11 desoxycorticosterone

(b) Desoxycorticosterone (synthesized)

~(c) 17 hydroxy 11 desoxycorticosterone

~(d) Amorphous fraction

(4) Estrogenic action³

(a) Estrone

(b) Estradiol

(c) Estrin

(5) Progestational action—progesterone

c Commercial extracts contain¹

(1) Various steroids which have carbohydrate as well as electrolytic action

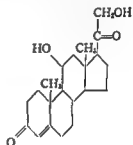
(2) Weak androgens

(3) Estrogens

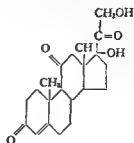
(4) Progesterone

2 Formulas of certain cortical compounds

a Corticosterone (compound B—Kendall, H—Reichstein)



b 17 hydroxy 11 dehydrocorticosterone (compound E—Kendall Fa—Reichstein, F—Wintersteiner and Pfaffner)



4 Performance of muscular work^{8 1 18} 31.33 42

a Adrenalectomized and nephrectomized rats are standardized as to

(1) Weight

(2) Diet

b A special apparatus is necessary for

(1) Stimulation of the muscles

(2) Recording results

■ Cortical hormones are injected

(1) At the beginning of muscular stimulation

(2) Again 6 hrs later

d Stimulation is continued either

(1) Until the muscle ceases to respond

(2) For a period of 24 hrs

■ The total number of recorder revolutions* for the 24 hr period is taken as an index of the efficacy of treatment

f Unit—the work equivalent of a 0.2 mg dose of 17 hydroxy 11 dehydrocorticosterone administered twice during the test

g A standard dosage response curve is established with 17 hydroxy 11 dehydrocorticosterone which permits the interpolation of work performance in units of the standard

h Method is specific for detection and estimation of biologic activity characteristic of the 11 oxygenated cortical steroids

5 Survival after adrenalectomy

a Dogs (adult)^{8 4 40 46}

(1) Animals are adrenalectomized in 2 stages

(2) Special care and diet are essential

(3) Hormone extract is given (0.5 cc/kg) in 2 equally divided doses twice a day

(4) Normal physiologic conditions are to be maintained as determined by

(a) Maintenance of body weight

(b) Blood nonprotein nitrogen (or urea)

(5) Unit—minimum daily kilogram dose of cortical hormone necessary to maintain a normal physiologic [maintenance of body weight and blood level of NPN (or urea)] state in an adrenal ectomized dog for a period of 7 to 10 days

(6) Test may be modified by basing the assay on⁷

(a) Appetite

(b) Body temperature

b Rats^{7 8 35}

(1) The number of days of survival after operation are determined

(2) Comparison is made with a group receiving hormone injections daily

(3) Unit—minimum dose of hormone which given subcutaneously daily for 20 days to 4 week old male rats (60 to 80 Gm) is sufficient to

(a) Protect at least 80 per cent of the rats

(b) Produce an average growth of at least 20 Gm for the 20 day period

c Other animals may be used^{8 57}

6 Survival after exposure to low temperature^{8-10 4 49 0}

a Male or female hooded adrenalectomized rats between 35 to 50 Gm

b Twelve to 24 hrs after adrenal ectomies food and water are removed and the rats are placed in the refrigerator at a temperature from -2° to -5 C

c Nine treated and 9 untreated animals are taken

d Hormone is administered subcutaneously in 3 doses with a period of 3 hrs between injections

e Unit—the minimum amount necessary to maintain life of 2.3 of the treated rats at a time when 2.3 of untreated controls succumb

f Test is fairly simple rapid and sensitive

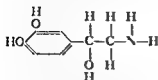
■ Mice may be used instead

7 Augmented potassium excretion^{8 61}

a Rats (dogs show similar effects), under certain established conditions

* Each recorder revolution represents approximately 4 cm of muscle shortening. Muscle is weighted with 100 Gm therefore each recorder revolution indicates about 400 Gm cm of work

- b Nor epinephrine 1 hydroxy 1 (3',4' dihydroxyphenyl) 2 aminoethane dihydroxyphenyl, arterenol levo active, dextro inactive)



3 Properties (epinephrine powder)¹³

- a Color—white or light brown
- b Odor—none
- c Taste—bitter
- d Activity destroyed by
 - (1) Copper
 - (2) Iron
 - (3) Zinc
 - (4) Other metals
- e Soluble in
 - (1) Water
 - (2) Alcohol
- f Insoluble in
 - (1) Chloroform
 - (2) Fixed and volatile oils
- g Solution—unstable
- h Dry form—stable
- i Oxidation retarded by excess acid
- j Decomposed by
 - (1) Air
 - (2) Light
 - (3) Heat

C HORMONE CONTENT IN BODY

1 Blood

- a Cortical hormones
 - (1) Peripheral—very small amounts
 - (2) With stress 1 cc of adrenal plasma may have 10 times the activity as that extracted from 1 Gm of gland¹⁶

b Epinephrine

- (1) Under resting conditions, concentration is less than one to one billion¹⁶
- (2) Peripheral venous blood contains 0000001 mg./l.⁷

2 Gland—epinephrine

- a Content of both amounts to about 10 mg (fatal dose of this hormone is 2 mg if given intravenously or 8 mg subcutaneously)¹⁶
- b Total secretion per day is about 6 Gm (man weighing 60 Kg.)⁷

VIII BIO ASSAY

A CORTICAL HORMONES

1 Resistance to typhoid vaccine^{8 44}

- a Three month old adrenalectomized rats are given intraperitoneal injections of concentrated cortical extract (20 to 40 Gm daily)
- b Minimal lethal dose (MLD) of the rats to typhoid vaccine is determined
- c Rat unit—the quantity of cortical extract necessary to raise the resistance of adrenalectomized rats sufficiently to survive the MLD of typhoid vaccine injected on the sixth day postoperatively

2 Resistance to histamine⁴

- a Adult, adrenalectomized rats are killed by 100 to 200 mg of histamine (ergotamine acid phosphate)/Kg when administered on the sixth day postoperatively (Normal rats survive 700 to 900 mg/Kg)
- b MLD of histamine for adrenalectomized 6 week old rats is between 150 to 250 mg/Kg of body weight
- c This is a better method than typhoid vaccine
- d Unit—the amount of cortical extract injected intraperitoneally into adrenalectomized, albino rats on fifth to sixth day postoperatively necessary to protect the animals against 200 mg of histamine

3 Maintenance of growth^{8 22 8 40 43}

- a Normal growth can be evidenced by the daily increase (of several grams) in weight
- b Injections of the cortical extract (from beef glands) are given intraperitoneally from first to seventh day to adrenalectomized 1 month old rats and growth is determined
- c Unit—the amount necessary to permit normal growth in a 40 to 50-Gm rat when given a single daily intraperitoneal injection
- d Growing animals require higher doses (relative to their size) than adults
- e Dogs cats or mice may be substituted

- d Method \equiv not employed now
- 13 Eosinophilic or lymphocytic response³
- Adrenocorticotropin injected
 - There is a decrease in circulating blood of
 - Eosinophils
 - Lymphocytes
- 14 Swimming test¹⁸
- Rats with weights tied to their tails are immersed in water
 - Submerging under the water indicates exact moment of exhaustion
 - Adrenalectomized animals given cortin injections show an increase in swimming power
 - Comparisons can be made of the swimming time¹ under various conditions
- 15 Anti insulin—the various cortical principles can be compared by determining the insulin resistance (number of convulsions) of mice^{2, 31}

B MEDULLARY HORMONES

- 1 Epinephrine
- Epinephrine can be determined by many biologic and chemical methods even when present in minute quantities but none of the methods is specific
 - Intestinal strip method (most commonly used)—inhibiting action on strip of intestinal muscle (1 part epinephrine to 500 millions of solution)^{5, 11}
 - Pressor changes in decerebrate cat^{23, 27}
 - Perfusion through isolated limb or hind limbs of decapitated frog resulting constriction serves as a measure of epinephrine content^{27, 33}
 - Auto-assay⁴
 - Reaction of animals blood on its own organs
 - Epinephrine determined by any other method
 - Anastomatic procedure⁴
 - Adrenal vein of normal animal anastomosed to jugular of adrenalectomized dog
 - Changes in splenic volume or other effects are determined
 - Effect of drug on
 - Uterus⁷
 - Denervated
 - Iris^{7, 1} or excised eye¹⁴
 - Heart^{19, 20}
 - Cava pocket⁷ method¹⁸
 - Amount of blood leaving adrenals/min
 - Concentration of epinephrine in this blood
 - Chromatographic methods—color reaction with^{1, 17, 18, 29, 39}
 - Ferric chloride
 - Ferricyanide
 - Iodine
 - Nishydrin
 - Persulfate
 - Nor epinephrine
 - Chromatographic methods— as above
 - Comparison with pharmacologic reactions of synthetic nor epinephrine or epinephrine nor epinephrine mixtures (see Table 48)²⁰

IX PATHOLOGY

A Gross—see Table 49 (following page)

B Microscopic

- Atrophy—see 40 IX B 1 a
- Hypoplasia—see 40 IX B 1 b
- Tuberculosis—see 40 IX B 1 c
- Amyloidosis—see 40 IX B 1 d
- Hemochromatosis—see 40 IX B 1 f
- Hyperplasia—see 42 IX B 1 a
- Adenoma—see 42 IX B 1 b
- Adenocarcinoma—see 42 IX B c
- Pheochromocytoma—see 44 IX B 1

C HISTOPATHOLOGY

- Hypophysectomy^{3, 4}
 - Fasciculata
 - Lipids and ketosteroids disappear
 - Mitochondria become smaller
 - Golgi nets are more compact
 - Glomerulosa—lipids and ketosteroids retained
- Adrenocorticotropin injections or stress (see 2 VI B 6 99)³
 - Fasciculata
 - Mitochondria swell
 - Golgi net enlarges
 - Ketosteroid content
 - Initially—decreases
 - Later—increases
 - Terminally—disappears

following injections of cortical extract, have definite changes in excretion

- (1) Decreased
 - (a) Phosphate
 - (b) Sodium
 - (c) Chloride

(2) Increased—potassium

b Results are very inconsistent

■ Sodium retention^{1, 40}

a Normal dogs must have special preparation and care in procedure

b Unknown material can be dissolved in peanut oil or 10 per cent ethyl alcohol and given subcutaneously

■ Desoxycorticosterone standardized as follows

(1) Response of each test animal determined following the injection of a given dose (0.6 to 0.8 mg)

(2) If dose injected gives less than 35 per cent or more than 65 per cent retention of sodium the test is repeated using a modified dose

d Sodium and chloride excretion are determined

e The normal electrolyte excretion (control level) of dogs is established for the 6 hr test period

f Control tests are done until the level is constant

g Percentage of sodium retention is calculated using the average of 2 controls immediately preceding the test as the normal level

h Unit—sodium retention defined as one tenth of the material which will cause equivalent sodium retention as 0.7 mg desoxycorticosterone in the same dog

i Calculation may be made by formula

$$\text{No of units} = \frac{\text{Per cent retention by unknown}}{\text{Per cent retention by 0.7 mg}} \times 10$$

9 Resistance to water intoxication¹⁸

a Adrenalectomized rats or dogs are used

b Animals are fasted and then a calculated amount of water is administered by a stomach tube

- Criteria of response determined by
 - (1) Rate of urinary excretion
 - (2) Occurrence of prostration
 - (3) Convulsions
 - (4) Death

d Various steroids are compared in this way

- Hormones are given in divided doses
 - (1) Subcutaneously
 - (2) Intraperitoneally

f Minimal dose for life maintenance can be determined for adrenocortical compounds

10 Glycogen deposition in liver^{9, 11, 35, 40-42, 47, 58}

a Standardized adrenalectomized mice are needed

b Injections are given subcutaneously at definite intervals

c Each mouse receives a total of 1.4 cc of extract containing 70 mg of glucose

d Livers are removed

(1) Glycogen is hydrolyzed

(2) Amount of glucose is determined

e Glycogen is expressed in terms of mg of liver glucose/100 Gm of mouse body weight

f Daily urinary excretion of corticoids in humans can be analyzed by this method

g Rats may be used

11 Resistance to shock¹⁴

a Adrenalectomized rats, 40 to 60 Gm which are tied down to a wire grid by all 4 legs for an hour develop shock and die in 4 hrs

b DOCA adrenal cortical extract and certain 11 oxygenated corticosteroids prolong their survival

c Typical dosage response curves may be obtained

12 Edema of perfused hind limbs^{30, 43}

a Perfusion methods for assaying potency of adrenal cortical extracts are unsuitable

b Frog and guinea pig hind legs are used

c There is little reason to expect adrenal cortical extracts through effects on capillary permeability to decrease edema in perfused animal hind limbs

X. CLASSIFICATION

A. COMPREHENSIVE LIST OF CHIEF FACTORS IN ENDOCRINE DISEASE—see 2 \ A

B. HORMONAL (primary and secondary)

1 Hyposecretion

a. Cortex

- (1) Sugar (' S) hormones—Addison's disease
- (2) Nitrogen (\) hormone
 - (a) Panhypopituitarism
 - (b) Addison's disease
 - (c) Primary myxedema
 - (d) Hyperthyroidism
- (3) Salt hormones
 - (a) Panhypopituitarism
 - (b) Addison's disease
- (4) Estrogens—hypopituitarism
- (5) Trichogens
 - (a) Primary myxedema
 - (b) Hyperthyroidism

b. Medulla—no known disease because of compensatory action of the sympathetic nervous system

2 Hypersecretion

a. Cortex

- (1) Sugar (S) hormones—Cushing's syndrome
- (2) Nitrogen (" \) hormone—adrenogenital syndrome
- (3) Salt hormones—Cushing's syndrome possibly
- (4) Estrogens—feminizing syndrome
- (5) Trichogens
 - (a) Primary myxedema rare
 - (b) Menopause
 - (c) Hypertrichosis

b. Medulla—epinephrines—paroxysmal or sustained hypertension in pheochromocytoma

3 Mixed—hyposecretion and hypersecretion

a. Cortex—adrenogenital syndrome with adrenal insufficiency due to hormonal

- (1) Sugar (S)—decrease
- (2) Nitrogen (\)—increase
- (3) Salt—decrease

b. Medulla—none recognized

C. CLINICAL

1 Hypofunction

a. Cortex

- (1) Addison's disease—primary cor

ticolysis¹ 4.3

- (2) Adrenal insufficiency secondary to pituitary disease

- (3) Congenitally small cortices

b. Medulla

- (1) No primary clinical syndrome has been recognized
- (2) Secondary to adrenal denervation (splanchnic resection)

c. Combined cortex and medulla

- (1) Addison's disease—classic
- (2) Adrenalectomy—removal of one gland when the other gland is
 - (a) Nonfunctioning
 - (b) Absent
- (3) Congenitally small adrenals
- (4) Status thymicolymphaticus
- (5) Associated with hyperplasia of adrenogenital syndrome

2 Hyperfunction

a. Cortex

- (1) Cushing's syndrome (predominantly hypersecretion of "S" hormones)

- (a) Fetal
- (b) Prepuberal
- (c) Postpuberal

- (2) Adrenogenital syndromes (androgenic hyperadrenal corticalism)¹¹

- (a) Fetal
 - [1] Early—pseudohermaphroditism (female)
 - [2] Late
 - [a] Masculinization in female without pseudomale external genitalia
 - [b] Precocious male

- (b) Prepuberal
 - [1] Masculinized female with enlarged clitoris
 - [2] Precocious male

- (c) Postpuberal—virilism in female

(3) Mixed entities

- (a) Cushing's syndrome combined with features of adrenogenital syndrome

- (b) Adrenal insufficiency and adrenogenital syndrome (included under hypofunction)

TABLE 49 SURGICAL PATHOLOGY

	SIZE	APPEARANCE	CAPSULE	CONSISTENCY	LOCATION	EXTENSION
Cortex						
Adenomas	Barely discernible to large single or multiple	Red or yellow mass	Intact	Hyperplastic nodules soft	Cortex	Other adrenal may be aplastic
Hypertrophy	Slight to size of kidney	Normal	Intact	Firm	Usual except when accessory or aberrant gland	None
Carcinoma	Small to large	Gray or gray yellow often hemorrhagic smooth or multiple nodules	May be broken through	Soft	Cortex	Adrenal and renal veins invaded to lymph nodes liver lung brain and opposite adrenal via lymph or blood direct extension to kidney
Medulla						
Pheochromocytoma	Small to large	When small—reddish with thin layer yellowish cortical tissue attached large size—gray to brown often hemorrhagic or cystic	Preserved	Soft ruptures easily	Medulla of adrenal retroperitoneal area along aorta sacro coccygeal region carotid body other aberrant sites	If malignant directly by blood stream or lymphatics

- b Glomerulosa—no change
- 3 Desoxycorticosterone⁴
- a Fasciculata—no change
- b Glomerulosa—lipid and ketosteroid content disappears
- 4 Adrenocortical or 11 oxycorticosteroid⁵
- a Fasciculata—ketosteroid droplets disappear
- b Glomerulosa—no change
- 5 Testosterone (rats) " "
- a Fasciculata—little effect
- b Glomerulosa—slight change
- c Reticularis—unaltered
- d X (male and female)—decreases especially in castrate animal
- 6 Estrogens⁷
- a Spayed guinea pig
- (1) Fasciculata—decreased
- (2) Glomerulosa—increased
- (3) Reticularis—increased
- b Rats (normal)
- (1) X zone¹
- (a) Male—reappearance of cells
- (b) Female—disappearance of cells
- (c) Lipoid substance produced
- (2) Gland (female) may increase⁸
- 7 Progesterone
- a Spayed guinea pig—all three zones are affected depending on amount administered
- (1) Small—increase⁷
- (2) Large—atrophy
- b Rats (female)—X zone shows no change⁹

XIII EXAMINATION OF THE PATIENT

The divergent clinical syndromes caused by dysfunction of the adrenal glands renders no simple and satisfactory plan of examination

A HYPADRENOCORTICALISM OR ADDISON'S DISEASE (see 40 \II)

1 History of

a Weakness

(1) Gradual

(2) Fairly rapid

b Anorexia

c Loss of weight

d Nausea

e Vomiting

f Diarrhea

g Abdominal pain

h Darkening of skin

i Loss of energy

j Familial tuberculosis

2 Physical status

a General

(1) Languor often

(2) Prostration in acute cases

(3) Evidence of weight loss

b Skin

(1) Loss of elasticity

(2) Pigmentation

(a) Light tan or chestnut brown color

(b) Look for increased pigment on

[1] Exposed surfaces

[2] Points of friction

[3] Scars

[4] Tongue

(c) Inspect mucous membranes of lips and mouth for patchy pigmentation

(d) Black freckles (ink spots) are important

■ Temperature is often subnormal in crisis

d Sexual hair in females

(1) Is scanty

(2) Regrows slowly when cut

e Heart sounds lack usual force

f Pulse is variable often thin

■ Blood pressure

(1) Variable usually low

(2) Normal or increased level in middle age does not exclude Addison's disease

h Splenic enlargement in some cases

i Lymph glands may be palpable especially after infection

j Muscular weakness can be demonstrated

3 Laboratory data

a Urinary chemical analyses^{7 8}

(1) Sugar Absent or present with associated diabetes mellitus

(2) Potassium Decreased

(3) Sodium Increased, until body depletion occurs

(4) Chlorides Increased until body depletion occurs

b Blood chemical analyses during crisis may be normal (because of hemoconcentration) or as follows^{7 8}

(1) Sugar (fasting) Decreased

(2) Nonprotein nitrogen Increased

(3) Urea nitrogen Increased

(4) Sodium Decreased

(5) Potassium Increased

(6) Chlorides Decreased

(7) Carbon dioxide combining power Decreased

c Glucose insulin and glucose insulin tolerance tests (see 103 I J)

(1) These are not necessary for routine diagnosis

(2) Hypoglycemic reactions are due to insulin sensitivity therefore insulin administration must be given with caution

d Urinary hormone assays (see 107 II A C III IV)

(1) 17 ketosteroids—very low an index of N hormone function

(2) 11 oxysteroids—absent an index of S hormones

4 Roentgenographic findings

a Skull should be checked for possible pituitary tumor especially if there is no pigmentation of the skin or mucous membranes

b Chest for tuberculosis

c Abdomen for adrenal

(1) Calcification

(2) Tumor

- (4) Feminizing syndromes (estrogenic hyperadrenal corticalism)—with the exceptions of feminization of the adult male and male pseudohermaphrodites, the following syndromes are more or less hypothetical^{2, 8}

(a) Fetal period

- [1] Female characteristics superimposed upon basically male organs—male pseudohermaphrodite

- [2] Precocious sexual development in female

(b) Prepubertal

- [1] Feminized boy
[2] Precocious sexual development in female

(c) Adult

- [1] Feminized male
[2] Hyperfeminized female⁽²⁾

- (5) Hypertrichosis* — excess hair growth in females without other masculinizing features

- b Medulla (hyperadrenalinism or hyperpinephrinism) — pheochromocytoma with paroxysmal or sustained hypertension

- c Mixed syndromes (hyperfunction and hypofunction)—adrenogenital syndrome and hypertension with pheochromocytoma^{4, 7}

D TUMORS⁹

1 Types

a Cortical

- (1) Adenoma—nonmalignant
(2) Carcinoma

b Medullary

- (1) Pheochromocytoma
(a) Benign
(b) Benign metastasizing
(c) Malignant (5 to 10%)
(2) Neuroblastoma or sympathoblastoma of various types—malignant

- (3) Ganglioneuroma—benign

- (4) Mixed tumors containing any or all elements of above

c Interstitial¹⁰

- (1) Sarcoma
(2) Lipoma
(3) Hemangioma
(4) Lymphangioma

2 Endocrine function

a Cortical tumors

- (1) No alteration
(2) Hyposecretion
(3) Hypersecretion

b Medullary tumors

- (1) No alteration
(2) Hypersecretion

c Interstitial cell

- (1) Usually no alteration
(2) Hypofunction—possible
(3) Hyperfunction—may be

XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION

A CORTEX

- 1 Anorexia
2 Weight loss
3 Asthenia
4 Hypotension

B MEDULLA—None

XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION

A CORTEX

- 1 Sugar (S) hormones
a Growth retardation in young
b Striae purplish
c Genital atrophy
d Osteoporosis
e Lympholysis
f Diabetes mellitus
2 Nitrogen ('N') hormone
a Growth acceleration in young
b Muscle mass—increased
c Acne
d Hypertrichosis
e Masculinization in varying degrees

3 Mineral hormones

- a Hypertension
b Salt retention

B MEDULLA—Hypertension

* While this is familial and racial in many instances the presence of excess urinary 17 ketosteroids points sufficiently to cortical hyperfunction in regard to hair producing hormones to warrant its inclusion here

- [2] Values for A which are less than 25 mean that Addison's disease is likely, providing nephritis has been excluded
- [3] If results are equivocal do salt deprivation test (see 39 XIII A 5 d)
- (4) Place of performance of test
- (a) Part I
- [1] Home
- [2] Office
- [3] Hospital
- (b) Part II
- [1] Office
- [2] Hospital
- (5) Pathophysiologic considerations in chronic adrenal insufficiency
- (a) Part I—failure to excrete ingested water at normal rate may be due to
- [1] Faulty gastro-intestinal absorption
- [2] Abnormal amounts of pituitary antidiuretic hormone in blood
- [3] Imbalance of water distribution in body
- [4] Impaired kidney excretion
- (b) Part II
- [1] Presence of azotemia is common
- [2] Inability to retain sodium or chloride
- (6) Test may become negative in Addisonian patients when treated with Cortisone but not with desoxycorticosterone
- (7) Test may be positive in
- (a) Pituitary insufficiency
- (b) Cushing's syndrome
- (c) Myxedema (longstanding)¹⁸
- (d) Hyperthyroidism
- (e) Hyperparathyroidism osteitis fibrosa cystica and renal damage
- (f) Normal people
- (g) Anorexia nervosa
- (h) Cachexia and allied disorders
- (i) Prolonged febrile illness
- (j) Sprue
- (k) Postgastrectomy
- (l) Acute rheumatoid arthritis
- (m) Renal disease
- (n) Postsympathectomy (dorso-lumbar)¹⁸
- (o) Orthostatic hypotension
- (p) Hepatic cirrhosis
- (q) Chronic calculous cholecystitis
- (r) Psychopathic personality
- (s) Neurologic disorders
- b Epinephrine test for anterior pituitary adrenocorticotrophic response⁸
- (1) Method
- (a) No food is taken after 8 00 P M
- (b) In the morning under fasting conditions a control eosinophil count is done on venous blood
- (c) Five cc of venous blood is drawn into a bottle containing special solution to prevent distortion of red cell volume
- (d) Solution
- | | |
|-------------------|--------|
| Ammonium | |
| oxalate | 1.2 Gm |
| Potassium oxalate | 0.8 Gm |
| Add distilled | |
| water to | 100 cc |
- (e) After obtaining sample shake immediately and gently
- (f) Specimen may be stored at temperature of 4° C up to 12 hrs
- (g) Epinephrine hydrochloride injected either
- [1] Intravenously over 1 hr—0.2 mg or 0.2 cc of 1:1,000 in 200 cc of saline
- [2] Subcutaneously—0.3 cc
- (h) Sample is drawn 4 hrs after the beginning of the administration of epinephrine
- (i) Food is taken after the test
- (j) Eosinophil count technic

5 Methods for special procedures

a Water test

(1) Indication — for determination of mineral hormonal function?⁸⁻¹¹

(2) Part I (see Charts 87 and 88)

(a) Method and directions (based on volume of urine—modified so that patient can do it at home)

[1] On day before test eat ordinary meals, but do not add salt to your food

[2] Do not eat or drink after 6 00 P M

[3] At 10 30 P M empty bladder, do not save the urine at this time

[4] Collect all the urine from then on until and including that passed at 7 30 A M

[5] Measure total urine in ounces

[6] Omit breakfast

[7] Drink 3 ounces of tap or warm water for each 10 lbs of body weight (example—if 120 lbs, drink 36 ounces)

[8] Drink entire amount in 20 min

[9] Note the time when all water is taken

[10] Empty bladder at 1 2, 3 and 4 hrs after that

[11] Lie down during entire test except to void

[12] Collect each amount separately and measure in ounces

[13] Bring in the record of [a] Ounces of urine passed during night

[b] Ounces of urine passed at 1, 2 3 and 4 hrs

(b) Test is not accurate if patient

[1] Cannot drink the required amount of water

[2] Vomits

[3] Does not follow instructions correctly (when performed at home)

(c) Interpretation

[1] If the volume of any single urine specimen exceeds that of nocturnal amount, Addison's disease is probably absent

[2] If the volume of one of the day specimens is less than that voided during the night, Addison's disease may or may not be present

[3] If one specimen is below 100 cc, Addison's disease is very likely

[4] Part II is performed, if Part I is indefinite

(3) Part II

(a) Method (based on chemical composition of blood and urine)

[1] Part I is completed first

[2] Fasting blood sample is drawn (under oil preferably)

[3] Plasma is analyzed for

[a] Urea

[b] Chloride

[4] Night urine (10 30 P M to 7 30 A M) is analyzed for

[a] Urea

[b] Chloride

[5] Largest volume of day urine is used in calculation

[6] Equation for A*

(b) Interpretation

[1] Values for A which are greater than 30 indicate that patient probably does not have Addison's disease

$$*A = \frac{\text{Urea in night urine (mg/100 cc)}}{\text{Urea in plasma (mg/100 cc)}} \times \frac{\text{Chloride in plasma in (mg/100 cc)}}{\text{Chloride in night urine (mg/100 cc)}} \times \frac{\text{Volume of day urine (cc)}}{\text{Volume of night urine (cc)}}$$

- [1] Inexperienced technician
- [2] Other factors possibly
- (b) Adequate adrenal cortical response if there is
 - [1] A fall of 50 per cent or more from the initial level of eosinophils
 - [2] An increase in the uric acid-creatinine ratio to a level above 50 per cent of the control
- (c) Variations in initial eosinophil count do not affect percentage of fall except during height of allergic eosinophilia when production exceeds peripheral destruction of eosinophils
- (d) False positives due to uric acid changes with
 - [1] Decreased renal clearance
 - [2] Abnormally high production of uric acid (gout leukemia)
- (e) Any condition causing acute stress may call out reserve of adrenal cortex and so gland cannot respond to further stimulation
- d Salt deprivation test for mineral hormone function? *
- (1) Method
 - (a) Low sodium diet for 3 days
 - [1] Chloride 0.95 Gm
 - [2] Sodium 0.59 Gm
 - [3] Potassium 4.10 Gm
 - (b) First day
 - [1] Free fluid intake
 - [2] In afternoon extra potassium (as citrate)
 - [a] Dose represents 0.033 Gm of potassium for each kilogram of body weight
 - [b] To convert potassium to grams of potassium citrate multiply by 2.8
 - (c) Second day
 - [1] Forty cc of liquid is taken/kg of body weight
 - [2] Repeat dose of potassium citrate
 - [3] Blood sample is taken in an oiled syringe at 8.00 A.M.
 - [4] Urine collected from 8.00 A.M. to 8.00 P.M.
 - (d) Third day
 - [1] Twenty cc. of liquid/kg of body weight is taken by 11.00 A.M.
 - [2] Blood sample is drawn in an oiled syringe at 10.00 A.M.
 - [3] Urine collected from
 - [a] 8.00 P.M. to 8.00 A.M.
 - [b] 8.00 A.M. to 12 N.
- (2) Results
 - (a) Blood plasma values for chloride sodium and potassium overlap those of the controls and so of little diagnostic value
 - (b) Concentration of chloride in urine of morning on third day is the most diagnostic part of test
 - [1] Addison's disease or adrenal insufficiency show values over 225 mg % (range 229 to 356)
 - [2] Adrenal insufficiency is unlikely in values less than 125 mg % (range 17 to 141)
 - [3] Values between the two
 - [a] Continue with restricted intake of sodium chloride
 - [b] Increase amount of potassium to equal a total of 9 Gm/24 hrs for 3 additional days or until crisis develops
 - (c) Urinary sodium of the third morning specimen (8.00 A.M. to 12.00 NOON) can be used for diagnosis
 - [1] Addison's disease—values of 206 mg % (range 165 to 282)

- [1] Special diluting solution
 - [a] Eosin (aqueous) 2 per cent 5 cc
 - Acetone 5 cc
 - Distilled water sufficient to make 100 cc
 - [b] Refrigerate and filter before use
 - [2] Oxalated venous blood is drawn into a white cell count pipet up to the 0.5 mark
 - [3] Pipet is shaken immediately gently only 30 times
 - [4] Chamber is filled with special solution
 - [5] Eosinophils counted after 3 min
 - [a] Levy chamber having a depth of 0.2 mm and ruled area of 16 sq mm is used
 - [b] Average of 4 chamber counts is determined
 - [c] Number of eosinophils per cubic millimeter equals 6.25 times the average chamber count
 - (2) Interpretation (see Chart 89)
 - (a) Patients with either Addison's disease or anterior pituitary insufficiency fail to show a decrease of 50 per cent or more in circulating eosinophils
 - (b) Acute allergy may prevent an adequate fall because of a rapid replacement by a hyperplastic bone marrow
 - (c) Complete reliance upon test is to be avoided
 - (3) Contraindication — arteriosclerotic cardiovascular disease
 - c Adrenocorticotropin (ACTH) test (Thorn) for adrenal cortical function of "S" hormones^{15, 20}
- (1) Method
 - (a) No food is given after 8:00 P.M. on the day preceding the test, but water may be taken as desired
 - (b) On the day of the test, 200 cc of water is given at
 - [1] 6:00 A.M.
 - [2] 8:00 A.M.
 - [3] 10:00 A.M.
 - (c) Urine specimen is collected from
 - [1] 6:00 A.M. to 8:00 A.M. (control)
 - [2] 9:00 A.M. to 12:00 P.M.
 - (d) Eosinophil count (see 4 c) is done at
 - [1] 8:00 A.M.
 - [2] 12:00 P.M.
 - (e) Twenty-five mg of purified adrenocorticotropin hormone is injected intramuscularly at 8:00 A.M. (after obtaining eosinophil count)
 - (f) There are no reactions except blanching of the skin and mild intestinal cramps due to the contamination with oxytocic principle
 - (g) Urine specimens
 - [1] Analyze by any standard method for
 - [a] Uric acid
 - [b] Creatinine
 - [2] Compute the percentage change in uric acid creatinine ratio
 - [3] Normal mean fasting uric acid creatinine ratio

[a] Male	0.43
[b] Female	0.59
[c] Mean	0.50
[d] Mean deviation	0.17
 - (h) Eosinophil count technique (as above)
 - (2) Interpretation (see Chart 90)
 - (a) Too much reliance should not be placed upon eosinophilic response due to inaccuracy of counting cells by

- {2} Incision 2 to 4 cm
- {3} Pockets prepared radially from incision by blunt dissection 2 to 3 cm in depth
- {4} One pellet implanted in each pocket after inspecting for bleeding
- {5} Incision closed with black silk

- (b) Greater increase (over 50%) in beta fraction with tumors than in hyperplasia (under 50%)¹⁰

- (c) Dehydroisoandrosterone is found in tumors rather than with hyperplasia¹

- (2) 11 oxysteroids—normal¹⁰

4 Roentgenographic findings

- a Skull—in children with precocious development to exclude
 - (1) Pinealoma
 - (2) Other intracranial disease
- b Hand wrist for bone age
- c Pyelograms for
 - (1) Kidney displacement
 - (2) Adrenal tumor
- d Air insufflation for outlining adrenal tumor or enlargement by presacral technic of Blackwood⁸ is safe and satisfactory

C PHEOCHROMOCYTOMA (see 44 \III)

1 History for episodes of unusual character

- a Pounding headache
- b Sweating
- c Palpitation
- d Substernal distress
- e Tremor
- f Apprehension
- g Duration—5 min to 16 hrs

2 Physical status

- a During attack—see 44 \II
- b Blood pressure may be
 - (1) Normal
 - (2) Elevated with
 - (a) Ocular fundi showing vascular changes as found in hypertension
 - (b) Cardiac enlargement
 - (c) Gallop rhythm possibly
- c Adrenal tumor may be palpable 12 per cent are outside adrenal area²²
- d Precipitation of attack by palpation or massage of tumor site

3 Laboratory data

- a Findings during acute paroxysm—see 44 VII
- b Routine urine and blood chemical analyses are usually not helpful, except to point to chronic vascular nephritis in cases with sustained hypertension

B ADRENOGENITAL SYNDROMES (see 42 \III)

1 History

- a Age of onset
- b Spurts of growth
- c Weight—gain common
- d Voice—changes
- e Hair growth—abnormal
- f Muscular feats—unusual for age
- g Psyche—altered
- h Sexual pattern—changed
- i Possible evidence of adrenal insufficiency, but with physical manifestations of adrenogenital syndrome

2 Physical status

- a Bodily contour generally masculine in type but feminization of males is a rare exception
- b Weight variable increased in most cases
- c Height age
 - (1) Advanced in childhood
 - (2) Retarded if sexual maturity occurs before usual age
- d Acne
- e Hair growth
 - (1) Abnormal
 - (2) Precocious
- f Breasts enlarge
- g Blood pressure
 - (1) Normal
 - (2) Increased
- h Abdominal tumor may be found
- i Genitalia
 - (1) Hypertrophy
 - (2) Atrophy of external organs (males)

3 Laboratory data

- a Blood chemical analyses reveal nothing unusual unless the syndrome is a mixed type
- b Urinary hormone assays
 - (1) 17 ketosteroids
 - (a) Increased in majority

[1] Special diluting solution

- [a] Eosin (aqueous) 2 per cent 5 cc
 Acetone 5 cc
 Distilled water sufficient to make 100 cc

[b] Refrigerate and filter before use

[2] Oxalated venous blood is drawn into a white cell count pipet up to the 0.5 mark

[3] Pipet is shaken immediately, gently, only 50 times

[4] Chamber is filled with special solution

[5] Eosinophils counted after 3 min

- [a] Levy chamber having a depth of 0.2 mm and ruled area of 16 sq mm is used

- [b] Average of 4 chamber counts is determined

- [c] Number of eosinophils per cubic millimeter equals 6.25 times the average chamber count

(2) Interpretation (see Chart 89)

- (a) Patients with either Addison's disease or anterior pituitary insufficiency fail to show a decrease of 50 per cent or more in circulating eosinophils

- (b) Acute allergy may prevent an adequate fall because of a rapid replacement by a hyperplastic bone marrow

- (c) Complete reliance upon test is to be avoided

(3) Contraindication — arteriosclerotic cardiovascular disease

- Adrenocorticotropin (ACTH) test (Thorn) for adrenal cortical function of "S" hormones^{15 29}

(1) Method

- (a) No food is given after 8:00 P.M. on the day preceding the test, but water may be taken as desired

- (b) On the day of the test, 200 cc of water is given at

[1] 6:00 A.M.

[2] 8:00 A.M.

[3] 10:00 A.M.

- (c) Urine specimen is collected from

[1] 6:00 A.M. to 8:00 A.M. (control)

[2] 9:00 A.M. to 12:00 Noon

- (d) Eosinophil count (see 4 c) is done at

[1] 8:00 A.M.

[2] 12:00 Noon

- (e) Twenty-five mg of purified adrenocorticotrophic hormone is injected intramuscularly at 8:00 A.M. (after obtaining eosinophil count)

- (f) There are no reactions except blanching of the skin and mild intestinal cramps due to the contamination with oxytocic principle

- (g) Urine specimens

[1] Analyze by any standard method for

[a] Uric acid

[b] Creatinine

[2] Compute the percentage change in uric acid creatinine ratio

[3] Normal mean fasting uric acid creatinine ratio

[a] Male 0.43

[b] Female 0.59

[c] Mean 0.50

[d] Mean deviation 0.17

- (h) Eosinophil count technique (see above)

(2) Interpretation (see Chart 90)

- (a) Too much reliance should not be placed upon eosinophilic response due to inaccuracy of counting cells by

- [1] Patient should be reclining
 - [2] Blood pressure cuff is placed on opposite arm
 - [3] Measurements of blood pressure taken several times 1 min apart before test drug is given
 - [4] Blood pressure is allowed to stabilize (20 min or so)
 - [5] Intravenous saline drip is started slowly through a 3 way stop cock
 - [6] Dose of dioxobenzane is 10 mg/sq meter body surface same as for basal metabolic rate or 0.25 mg/kg of body weight
 - [7] Dioxobenzane solution introduced through 3 way stop cock taking 2 min to inject it
 - [8] Blood pressure readings are then taken at
 - [a] One half min intervals for 5 min
 - [b] One min intervals until blood pressure returns to normal
- (b) Dibenamine test^{9 10 31}
- [1] Procedure as above
 - [2] Dosage
 - [a] Five to 7 mg/kg of body weight
 - [b] Maximum regardless of weight is 500 mg
 - [3] Dibenamine is added to 300 to 500 cc of saline
 - [4] Rate of flow—total dose should take 1 hr (not over 8 cc/min)
 - [5] Blood pressure readings as above
 - [6] If pressure falls significantly stop solution especially if near normal levels
 - [7] Effect of drug may last several days
- (6) Interpretation (see 39 VI B 2)
- (a) Dioxobenzane test (see Chart 93)
 - [1] Effect of circulating epinephrine is neutralized with a resulting fall in blood pressure
 - [2] Extent of drop is thought to parallel the amount of circulating epinephrine
 - [3] Small initial drops in pressure lasting up to 2 min are not significant
 - [4] Positive test is probable when there is a sustained fall in pressure lasting at least 7 min
 - [5] If the blood pressure is plotted on square millimeter paper against minutes the area included below the base line of the initial blood pressure may be expressed in millimeter minutes
 - [6] False negative tests—certain cases of pheochromocytoma fail to show a decrease in blood pressure^{11 12}
 - [7] False positive result—one reported diagnosis not proven⁷
 - (b) Dibenamine test (see Chart 92)
 - [1] Positive test when there is a significant lowering of pressure
 - [2] Experience with this preparation is limited
 - (7) Toxic and undesirable reactions
 - (a) Dangerous reactions are possible hence care should be exercised in administering these preparations
 - (b) Dosages recommended probably should be reduced on first trial of these drugs in order to test response
 - (c) Reactions⁹
 - [1] Marked rise in hypertensive patients of systolic and diastolic blood pressures
 - [2] Palpitation
 - [3] Tachycardia
 - [4] Precordial pain

- [2] Control group—values of 22.4 mg % (range 6 to 85)
- [3] More difficult to do in most laboratories, and therefore chloride determination is utilized
- (3) Dangers—adrenal crisis may develop, and therefore test should be performed in hospital
 - (a) Intravenous injection should be
 - [1] On hand for emergency
 - [2] Given at end of each test
 - (b) Solution of 1,000 cc sterile water with
 - [1] Dextrose 50 Gm
 - [2] Sodium chloride 10 Gm
 - [3] Sodium citrate 5 Gm
 - [4] Cortical extract 20 cc
- e Potassium tolerance³⁰
 - (1) Indication—aid in doubtful cases of adrenal cortical insufficiency
 - (2) Method
 - (a) No breakfast
 - (b) Blood sample collected to determine fasting serum potassium
 - (c) Dosage of potassium salt to be taken orally is 10 mg/kg of body weight
 - (d) Blood samples are collected every half hour for two hours
 - Caution—severe crisis may occur!
 - (3) Results
 - (a) Normal—20 to 40 mg % increase in $\frac{1}{2}$ hr, with a return to normal by $1\frac{1}{2}$ to 2 hrs
 - (b) Adrenal insufficiency—much greater rise and stays there for longer period
 - (c) Inconstant
- f Techniques for pellet implantation¹⁷
 - (1) Locations—in subcutaneous tissue of
 - (a) Anterior thighs
 - (b) Abdomen
 - (c) Axillae
 - (d) Infrascapulae
 - (2) Methods
 - (a) "Medical" (office procedure) (see Fig 269)
 - [1] Skin prepared with
 - [a] Iodine
 - [b] Alcohol
 - [2] Intradermal infiltration of area of incision with procaine
 - [3] Subcutaneous infiltration for 3 to 4 cm in region of trocar thrusts
 - [4] Incision $\frac{3}{8}$ to $\frac{1}{2}$ in
 - [5] Abdominal or hydrocele trocar thrust in lower subcutaneous region horizontally for 3 in
 - [6] Stilet withdrawn
 - [7] Pellets
 - [a] Dipped in sterile saline
 - [b] Rolled lightly in sulfa powder
 - [8] One pellet
 - [a] Inserted into lumen of trocar
 - [b] Pushed through with stilet
 - [9] Trocar withdrawn $\frac{1}{2}$ to 1 in then second pellet implanted
 - [10] Only 2 pellets are implanted in 1 pocket
 - [11] New pockets are made in other directions if additional pellets are to be inserted at this time
 - [12] Incision edges are approximated by drawing skin tightly with a strip of adhesive which is applied transversely
 - [13] Thick gauze pad is placed over adhesive holding edges together
 - [14] Dressing and adhesive are removed in 4 to 5 days
 - (b) Surgical
 - [1] Skin prepared and infiltrated as above

- 23 Eustachius Bartholomaeus *De glandulis quae renibus incumbunt in Opuscula anatomica Vinctive Luchinus 1564*
- 24 Ferribee J W Ragan C, Atchley D W and Loeb R E Desoxycorticosterone esters certain effects in the treatment of Addison's disease JAMA 113 1725 1731 (Nov.) 1939
- 25 Fraenkel S Beiträge zur Physiologie und physiologischen chemie der Nebenniere Wien Med Bl 111 211 228 246 1896
- 26 Friderichsen C Nebennieren Apoplexie bei Kleinen Kindern Jahrb f Kinderb 87 109 125 1918
- 27 Goodhart J F Simple atrophy of supra renal capsules accompanied by melasma supra renale and other symptoms of Addison's disease Tr Path Soc. London 33 340 345 1882
- 28 Goodsur J On the supra renal thymus and thyroid bodies Philos Tr 136 633 641 1846
- 29 Gulliver G Notice on Mr Gulliver's observations on the thymus and mesenteric glands on the chyle and on the supra renal glands Dublin Medical Press 3 11 (Jan.) 1840
- 30 Harrop G A Weinstein A Soffer L J and Trescher J H The diagnosis and treatment of Addison's disease JAMA 100 1870-1875 (June) 1933
- 31 Hartman F A MacArthur C G and Hartman W E A substance which prolongs the life of adrenalectomized cat Proc Soc Exper Biol & Med 25 69 70 (Oct.) 1927
- 32 Heale F J Ueber das Gewebe der Nebenniere und der Hypophyse Ztschr f Rationelle Med 24 143 152, 1865
- 33 Heppner C L Über den wahren Hermaphroditismus beim menschen Arch f Anat Physiol u wissensch Med Leipzig pp 679 717 1850
- 34 Holmes G M A case of virilism associated with a suprarenal tumor recovery after its removal Quart J Med 18 143 152 (Jan.) 1925
- 35 Hutchinson R On suprarenal sarcoma in children with melasias in the skull Quart J Med 1 33 38 (Oct.) 1907
- 36 Kendall E C Lecture before American Chemical Society Mass Institute of Technology April 13 1950
- 37 Kendall E C Mason H L McEwen B F Myers C S and Moelich G A Isolation in crystalline form of the hormone essential to life from the suprarenal cortex its chemical nature and physiologic properties Proc Staff Meet Mayo Clin 9 245 250 (Apr.) 1934
- 38 Labbé E M Tisel J and Doumer Crises soudaines et hypertension paroxysmique en rapport avec une tumeur urénale Bull Soc med hop Paris 46 982 990 (June) 1912
- 39 Little E G Cases of purpura ending fatally associated with hemorrhage into the suprarenal capsules Brit J Derm 13 445-467 (Dec.) 1901
- 40 Loeb R F Chemical changes in the blood in Addison's disease Science 76 420 421 (Nov.) 1932
- 41 Marshall E H Jr and Davis D M The influence of the adrenals on the kidneys J Pharmacol & Exper Therap 8 525 550 (Sept.) 1916
- 42 Mayo C H Paroxysmal hypertension with tumor of retroperitoneal nerve report of case JAMA 89 1047 1050 (Sept.) 1927
- 43 Moore B On the chemical nature of a physiologically active substance occurring in the suprarenal gland Proc. Physiol Soc London 1895 pp xxi xxi
- 44 Neusser E Die Erkrankungen der Nebennieren Spec Path u Therap Nothnagel Wien Pt 3 28 1 98 1897
- 45 Oliver G and Schafer E A The physiological effects of extracts of the suprarenal capsules J Physiol 11 230 2 9 1895
- 46 Otto A W Seltene Beobachtungen zur Anatomie Physiologie und Pathologie Breslau Hofmeister 1816 pp 139 140
- 47 Pepper W A study of congenital sarcoma of the liver and suprarenal with report of a case, Am J Med Sc. 121 287 299 (Mar.) 1901
- 48 Perla D and Gottesman J M Substance in urine of normal human adults that raises resistance of suprarenalectomized rats Proc Soc Exper Biol & Med 111 1024 1027 (June) 1931
- 49 Pfiffner J J and Swingle W W The preparation of an active extract of the suprarenal cortex Anat Rec. 44 225 (Dec.) 1929
- 50 Pincoffs M C A case of paroxysmal hypertension associated with suprarenal tumor Tr Am A Physicians 44 295 299 1929
- 51 Porges O Ueber Hypoglykämie bei Morbus Addison sowie bei nebennierenlosen Hunden Ztschr klin Med 111 341 349 1909
- 52 Riouan J Oeuvres anatomiques Paris 1629
- 53 Rogoff J M and Stewart, G N Suprarenal cortical extracts in suprarenal insufficiency (Addison's disease) JAMA 92 1569 1571 (May) 1929
- 54 — The influence of adrenal extracts in the survival period of adrenalectomized dogs Science 66 327 328 (Oct.) 1927
- 55 Roux quoted by Von der Mühl R Contributions à l'étude des paraneuroses de la surrenale Lausanne Vauvey Burnier these 1928
- 56 Shipley A M Paroxysmal hypertension associated with tumor of suprarenal Ann Surg 90 742 749 (Oct.) 1929
- 57 Simpson S L The use of synthetic desoxy corticosterone acetate in Addison's disease Lancet 2 557 558 (Sept.) 1938
- 58 Steiger M and Reichstein T Partial synthesis of a crystallized compound with the biological activity of the adrenal cortical hormone Nature 139 925 926 (May) 1937
- 59 Stewart G N So called biological tests for adrenalin in blood with some observations on arterial hypertension J Exper Med 14 371 400 (Oct.) 1911
- 60 Stolz F Über adrenalin und Alkylaminoacetbenzocatechin Berichte d Deutsch chem Gesell 37 4149 4154 1904
- 61 Szent Gyorgyi A Observations of the functions of peroxidase systems and the chemistry of the adrenal cortex Biochem J 22 1387 1409 (June) 1928
- 62 Takamine J Adrenalin the active principle of the suprarenal glands and its mode of preparation Am J Pharm 73 525 531 (Nov.) 1901
- 63 Thoen G W Howard R P Emerson K Jr and Frier W M Treatment of Addison's disease with pellets of crystalline adrenal cortical hormone implanted subcutaneously Bull Johns Hopkins Ho p 64 339 365 (May) 1939
- 64 Thornton quoted by Young H H Genital Abnormalities Hermaphroditism and Related

- Basal metabolic rate is elevated when blood pressure is increased
- d Urinary hormone assay for epinephrine and nor epinephrine¹⁰
 - (1) Normal—20 to 40 micrograms/24 hrs
 - (2) Pheochromocytoma—up to 1,240 micrograms/24 hrs
- 4 Methods for special procedures
 - a Induction of paroxysm of hypertension by use of drugs^{4 5 14 15}
 - (1) Comment
 - (a) The danger of using certain drugs in patients with pheochromocytoma has frequently been pointed out and should be avoided in
 - [1] Severe cases
 - [2] Elderly people
 - (b) Basal blood pressure should be obtained first
 - (c) Avertin rectal anesthesia may be used to eliminate emotional variations in pressure
 - (d) Readings are taken at intervals of 1 min for 20 min
 - (e) False negatives and false positives may occur
 - (2) The following have been given to provoke an attack
 - (a) Adrenalin
 - [1] One to 1½ cc (1:1000) subcutaneously
 - [2] Induction of hypertension is possible although unusual resistance to this drug may exist²
 - (b) Histamine acid phosphate or hydrochloride⁴
 - [1] Dilute 1 cc of this solution in 9 cc of water
 - [2] Inject ¼ or ½ cc (0.025 or 0.05 mg) intravenously
 - [3] Antidote—adrenalin ½ cc intravenously
 - (c) Mecholyl (acetyl β methyl choline chloride—see Chart 91)¹⁴
 - [1] Twenty five mg subcutaneously in forearm (below BP Cuff)
 - [2] For severe reaction
 - [a] Atropine sulfate gr ⅓ intravenously
 - [b] Blood pressure cuff or tourniquet should be applied to prevent further absorption
 - (d) Etamon (tetraethylammonium bromide or chloride)⁶
 - [1] Three cc intravenously, supine position*
 - [2] Instead of a sustained drop in blood pressure, a fluctuating fall followed by a rise may take place if pheochromocytoma is present
 - [3] Adrenalin (½ cc intravenously) may be used for postural hypotension
 - (e) Insulin tolerance test—may be helpful if diabetes is present (see 103 I J 2)
 - b Anti epinephrine tests
 - (1) Indications
 - (a) Differentiation of hypertension due to pheochromocytoma from other types
 - (b) Prevention of hypertensive crisis on manipulation or removal of pheochromocytoma
 - (2) Several preparations are available whose actions are chiefly adrenolytic
 - (3) Pharmacologic action is to produce a high degree of reversible block to the stimulation of the adrenergic receptor cells to sympathetic nerve impulses or epinephrine
 - (4) Preparations
 - (a) Dioxobenzane (benzodioxane benodaine 2 [1 piperidylmethyl] 14 benzodioxane or 933 F)
 - (b) Dibenamine (N N dibenzyl β chloroethylamine hydrochloride)
 - (5) Technics^{2 3 12 13 16 17}
 - (a) Dioxobenzane test

* Patient should not stand during procedure or until weakness is gone. An increase or decrease in blood pressure level may be regulated by lying or sitting position.

- Metabolism in Cold Spring Harbor Symposia on Quantitative Biology Cold Spring Harbor L I 5 357 363 1937
- 9 Cannon W B McIver W A and Bliss S W Studies on the conditions of activity in endocrine glands. VII A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia, *Am J Physiol* 69 46 66 (June) 1924
 - 10 Cannon W B and Rosenbuth A Autonomic neuro effector systems *Am J Physiol* 104 357 363 (June) 1933
 - 11 Carrier E H Studies on physiology of the capillaries reaction of the human skin capillaries to drugs and other stimuli *Am J Physiol* 61 528 547 (Aug) 1922
 - 12 Castleden L I M Effect of adrenalin on serum potassium level in man *Clin Sc* 3 241 245 (Apr) 1938
 - 13 Chass, H Ranges, H A Goldring W and Smith H W The control of renal blood flow and glomerular filtration in normal man *J Clin Investigation* 17 683 697 (Sept) 1938
 - 14 Cori C F Mammalian carbohydrate metabolism *Physiol Rev* 11 143 275 (Apr) 1931
 - 15 — Symposium on carbohydrate metabolism: glycogen breakdown and synthesis in animal tissues *Endocrinology* 26 285 296 (Feb) 1940
 - 16 Cori C F and Cori G T Mechanism of epinephrine action influence of epinephrine on carbohydrate metabolism of fasting rats with note on new formation of carbohydrates *J Biol Chem* 79 309 319 (Sept) 1918
 - 17 D'Silva J L Action of adrenaline like substances on the serum potassium *J Physiol* 108 218 225 (Feb) 1949
 - 18 Dubois C and Polonovski M Influence of epinephrin on urea in blood *Compt rend Soc de biol* 91 293 295 (July) 1924
 - 19 Edmunds C W Some vasomotor reactions of the liver *J Pharmacol & Exper Therap* 6 569 590 1915
 - 20 Ferrebee, J W Parker O Carnes W H Gentry M K Atchley D W., and Loeb R F Certain effects of desoxycorticosterone development of diabetes insipidus and replacement of muscle potassium by sodium in normal dogs *Am J Physiol* 135 230 237 (Dec) 1941
 - 21 Ferrebee J W Ragan C Atchley D W and Loeb R F Desoxycorticosterone esters certain effects in treatment of Addison's disease *JAMA* 113 1725 1731 (Nov) 1939
 - 22 Forsham P H Thorn G W and Bergner G E Metabolic changes induced by synthetic 11 dehydrocorticosterone acetate, *Am J Med* 1 105 134 (Aug) 1946
 - 23 Garrey W H and Bryan W R Variations in white blood cell counts *Physiol Rev* 15 597 638 (Oct) 1935
 - 24 Goldenberg N Faber M Alston E J and Chargoif H C Evidence for the occurrence of nor epinephrine in the adrenal medulla *Science* 109 534 535 (May) 1949
 - 25 Goldenberg M Pines K L Baldwin E de F Greene D G., and Roh C E The hemodynamic response of man to nor epinephrine and epinephrine and its relation to the problem of hypertension *Am J Med* 5 92 806 (Dec) 1948
 - 26 Grasop H O and Deane H W Cytochemical evidence for cessation of hormone production in zona glomerulosa of rats adrenal cortex after prolonged treatment with desoxycorticosterone acetate *Endocrinology* 40 417-425 (June) 1947
 - 27 Griffith F R Jr Omachi A Lockwood J E and Loomis T A Effect of intravenous adrenalin on blood flow sugar retention lactate output and respiratory metabolism of peripheral (leg) tissues in anesthetized cat *Am J Physiol* 149 64 76 (Apr) 1947
 - 28 Grollman A Harrison T R and Williams J R Jr Effect of various steroid derivatives on blood pressure of rat *J Pharmacol & Exper Therap* 69 149 155 (June) 1940
 - 29 Gruber C M The effect of epinephrine on excised strips of frog's digestive tracts *J Pharmacol & Exper Therap* 20 321 357 1923
 - 30 Harrop G A Soffer L J Ellsworth R and Trescher J H Studies on suprarenal cortex plasma electrolytes and electrolyte excretion during suprarenal insufficiency in dog *J Exper Med* 58 17 38 (July) 1933
 - 31 Hartman F A Brownell K A and Thatcher J S A new hormone of the adrenal cortex *J Clin Endocrinol* 7 461 (June) 1947
 - 32 Ho lins R G The splanchnic effect of epinephrine upon the intestines *Am J Physiol* 29 363 366 1912
 - 33 Hoskins R G and Gunning R E L The effects of adrenin on the distribution of the blood II Volume changes and venous discharge in the spleen *Am J Physiol* 43 298 303 (May) 1917
 - 34 Hoskins R G and McClure C W The relation of the adrenal glands to blood pressure *Am J Physiol* 30 192 195 1912
 - 35 Ingle M J Work capacity of adrenalectomized rat treated with cortin *Am J Physiol* 116 622 675 (Aug) 1936
 - 36 — Work performance of adrenalectomized rats treated with corticosterone ad chemically related compounds *Endocrinology* 26 472 477 (Mar) 1940
 - 37 — The Chemistry and Physiology of Hormones *Am Assoc for Advancement of Science* Washington D C 1944 pp 103
 - 38 — Conference on Metabolic Aspects of Convalescence including Bone and Wound Healing 13th Meeting Naushon Island Woods Hole June 10 11 New York Josiah Macy Jr Foundation 1946 pp 117 134
 - 39 Ingle D J Sheppard R Oberle E A and Kuznetsov M H Comparison of acute effects of corticosterone and 17 hydroxycorticosterone on body weight and urinary excretion of sodium chloride potassium nitrogen and glucose in normal rat *Endocrinology* 39 52 57 (July) 1946
 - 40 Kallreider N L Meneely G R and Allen J R Effect of epinephrine on volume of blood *J Clin Investigation* 21 339 345 (May) 1942
 - 41 Kaplan D M On the hypodermic use of adrenalin chloride in the treatment of aortic aneurysms *Med News* 100 871 875 1905
 - 42 Kendall E C Function of adrenal cortex *Proc Staff Meet Mayo Clin* 15 29 304 (May) 1940
 - 43 — The adrenal cortex *Arch Path* 32 474 501 (Sept) 1941
 - 44 — The adrenal cortex *Ann New York Acad Sc* 50 540 547 (June) 1949
 - 45 Keys A Response of plasma potassium level

- [5] Hyperpnea
- [6] Headache
- [7] Fright
- [8] Nervousness
- [9] Cold extremities
- [10] Flushing
- [11] Nausea
- c Cold pressor test¹⁸
 - (1) Indication—to determine response of blood pressure and vasomotor irritability to cold
 - (2) Method
 - (a) Subject should rest for 20 min (omit sedation)
 - (b) Blood pressure is taken every 5 min until a constant level is reached
 - (c) One hand is immersed (above wrist) into ice water for 1 min blood pressure (using opposite arm) read at 30, 60 and every 120 sec until highest level obtained

(3) Results

- (a) Normal—minimal response (rarely rise of 10 mm mercury) in systolic and diastolic pressure to local cold stimuli
- (b) Pheochromocytoma—response may be
 - [1] Normal
 - [2] Hypertensive
- (c) Hypertension (organic forms)
 - [1] Systolic and diastolic pressures rise
 - [2] Delay in return of blood pressure to basal level
- 5 Roentgenographic findings
 - a Chest—for intrathoracic tumor²²
 - b Air insufflation is advisable, if necessary, presacral technic⁶
 - c Pyelogram for
 - (1) Adrenal tumor
 - (2) Kidney displacement

REFERENCES

I HISTORY

- 1 Abel J J On the blood pressure raising constituent of the suprarenal capsule *Johns Hopkins Hosp Bull* 8 151 157 (July) 1897
- 2 Addison T Anaemia—disease of the suprarenal capsules *London Med Gaz* 43 512 518 1849
- 3 Aldrich T B Preliminary report on active principle of suprarenal gland *Am J Physiol* 5 457 461 (Aug) 1901
- 4 Apert E Dystrophies en relation avec les lésions de capsules surrénales hirsutisme et progénia *Bull Soc pédiat de Paris* 12 501 1910
- 5 Bartholinus Thomas *Anatomia Lugdunum Bat Hackum* 1651
- 6 Baumann E J and Kurland S Changes in inorganic constituents of blood in suprarenal ectomized cats and rabbits *J Biol Chem* 71 281 302 (Jan) 1927
- 7 Beer E King F H and Prazmetel M Pheochromocytoma with demonstration of pressor (adrenalin) substance in blood preoperatively during hypertensive crises *Ann Surg* 106 85 91 (July) 1937
- 8 Berdez Contribution à l'étude des tumeurs des capsules surrénales *Arch d med Exper et anat path* 4 414 1892
- 9 Bergmann quoted by Grollman A *The Adrenals* Baltimore Williams & Wilkins 1936 ■ 4
- 10 Bevan and Romkild quoted by Bulloch W and Sequeira J H On the relation of the suprarenal capsules to the sexual organs *Tr Path Soc London* 56 189 208 1905
- 11 Bittorf A Nebennierentumor und Geschlechtsdrüsen—ausfall beim Manne *A Berl klin Wchenschr* 56 776 (Aug) 1919
- 12 Britton S W, and Silvette H *The Adrenal Cortex and Carbohydrate Metabolism in Cold Spring Harbor Symposia on Quantitative Biology* Cold Spring Harbor, L I New York The Biological Laboratory Vol 5 1937 pp 35, 359
- 13 Broster L R and Vines H W *The Adrenal Cortex a Surgical and Pathological Study* London Lewis 1933
- 14 Brown Sequard C M *Recherches expérimentales sur la physiologie et la pathologie des capsules surrénales* *Arch gen de med* 5^e sér 8 385 401 572 598 1856
- 15 Bulloch W and Sequeira J H On the relation of the suprarenal capsules to the sexual organs *Tr Path Soc London* 56 189 208 1905
- 16 Cannon W B *Bodily changes in fear hunger pain and rage* New York Appleton 1915
- 17 Combe J S History of a case of anaemia *Tr Med Chir Soc Edinburgh* 1 194 204 1824
- 18 Cook W quoted by Bulloch W and Sequeira J H On the relation of the suprarenal capsules to the sexual organs *Tr Path Soc London* 56 189 208 1905
- 19 de Crecchio L S Sopra un caso di apparenza virile in una donna Morgagni *Napoli* 7 151 185 1865
- 20 Dijkhuizen R K and Behr E Adrenal hypertrophy in infants new clinical entity of neonatal period *Acta paediat* 27 299 295 1940
- 21 Duncan L E Jr Semans J H and Howard J E Adrenal medullary tumor (pheochromocytoma) and diabetes mellitus disappearance of diabetes after removal of tumor *Ann Int Med* 20 815 821 (May) 1944
- 22 Ecker A *Der feine Bau der Nebennieren beim Menschen und den vier Wirbelthier Klassen* Braunschweig 1846

- 11 Wang F C and Vezar M Comparison between glyco-genetic property of desoxycorticosterone 11 dehydro 17 hydroxycorticosterone (Compound E) and adrenal cortical extract Am J Physiol 159 263 68 (Nov) 1949
 - 12 Watkins O and Smith G L Biochemical studies on effect of adrenalin upon nitrogen metabolism of rabbits Am J Physiol 96 28 34 (Jan) 1931
 - 13 Wells B B Influence of crystalline compounds separated from adrenal cortex on glucocorticogenesis Proc Staff Meet Mayo Clin 15 294 297 (May) 1940
 - 14 Williams H L and Watson E M Influence of hormones upon phos-phatase content of rat femurs Endocrinology 29 250-257 (Aug) 1943
 - 15 Wintersteiner O and Pfäffler J J Chemical studies on adrenal cortex isolation of 2 new physiologically inactive compounds J Biol Chem 116 291 305 (Nov) 1936
- C Adrenalectomy**
- 1 Anderson M Joseph S and Herning V Salt after adrenalectomy growth and survival of adrenalectomized rats given various levels of NaCl Proc. Soc. Exper Biol & Med 44 477 481 (June) 1940
 - 2 Baur P C, Jr Cloney E and Albright F Effect of cortical hormone in preventing extreme drop in colonic temperature displayed by hypophysectomized rats upon exposure to cold with preliminary observations upon effect of hypophyseal and other hormones Am J Physiol 104 489 501 (May) 1933
 - 3 Britten S W Adrenal insufficiency and related considerations, Physiol Rev 10 617 682 (Oct) 1930
 - 4 — The Adrenal Cortex and Carbohydrate Metabolism in Cold Spring Harbor Symp on Quant Biol Cold Spring Harbor L I 5 357 361 1937
 - 5 Cope O Brenizer A G Jr., and Folderman H. Capillary permeability and adrenal cortex studies of cervical lymph in adrenalectomized dog Am J Physiol 137 69 8 (Aug) 1942
 - 6 Dennis C and Wood E H Intestinal absorption in adrenalectomized dog Am J Physiol 129 182 190 (Apr) 1940
 - 7 Emery P E and Gottsch L G Studies on pituitary implants and extracts in adrenalectomized rats, Endocrinology 28 321 324 (Feb) 1941
 - 8 Freed S C and Lindner E Effect of steroids of adrenal cortex and ovary on capillary permeability Am J Physiol 134 258 262 (Sept) 1941
 - 9 Friedman M Somkin E and Oppenheimer E T Relation of renin to adrenal gland Am J Physiol 128 481-487 (Feb) 1940
 - 10 Gaunt R Endocrine factors in water diuresis and water intoxication Tr New York Acad Sc 6 1 9 187 (Apr) 1944
 - 11 — Animal experiments relating to water diuresis Tests for adrenal insufficiency J Clin Endocrinol 6 595 606 (Sept) 1946
 - 12 Gaunt R and Tobin C E Lactation in adrenalectomized rats Am J Physiol 115 588 598 (May) 1936
 - 13 Graham J S Adrenal cortex and blood pressure response to carbon arc irradiation Am J Physiol 139 604 611 (Aug) 1943
 - 14 Grollman A Harrison T R and Williams J R Jr Effect of various steroid derivatives on blood pressure of rat J Pharmacol & Exper Therap 68 149 155 (June) 1940
 - 15 Harrop G A Jr Soifer L J, Ellsworth R., and Trescher J H Plasma electrolytes and electrolyte excretion during suprarenal insufficiency in dog J Exper Med 88 17 38 (July) 1933
 - 16 Hartman F A Brownell A A., and Crosby A A Relation of cortis to maintenance of body temperature Am J Physiol 98 674 686 (Nov) 1931
 - 17 Hartman M A., Lewis L A Thatcher J S., and Street H H Effect of adrenal factors on plasma proteins Endocrinology 31 287 294 (Sept) 1942
 - 18 Hartman F A Smith D E and Lewis L A Adrenal functions in opossum Endocrinology 32 340 344 (Apr) 1943
 - 19 Hartman F A and Spoor H J Cortis and Na factor of the adrenal Endocrinology 26 871 8 8 (May) 1940
 - 20 Hechter O Effect of histamine upon capillary permeability in skin and muscle of normal and adrenalectomized rats Endocrinology 32 135 139 (Feb) 1943
 - 21 Huggins C and Scott W W Bilateral adrenalectomy in prostatic cancer clinical features and urinary excretion of 17 keto steroids and estrogen Ann Surg 122 1031 1041 (Dec) 1945
 - 22 Ingle D J The Chemistry and Physiology of Hormones Am Assoc. Advancement Sc Washington D C., 1944 pp 83 103
 - 23 Leric H and Uylert, I E Influence of adrenals on bone growth Acta brev Neerland 9 121 123 (May) 1939
 - 24 Loeb R L The adrenal cortex and electrolyte behavior Harvey Lect. (1941 1942) 38 100-118 1942
 - 25 Long C V H Katso B and Fry E G Adrenal cortex and carbohydrate metabolism Endocrinology 26 309 344 (Feb) 1940
 - 26 Marine D Physiology and principal interrelations of thyroid, J.A.M.A. 104 2250-2255 (June) 1935
 - 27 Marine D and Baumann E J Effect of suprarenal insufficiency (by removal) in thyroidectomized rabbits, Am J Physiol 59 353 368 (Feb) 1922
 - 28 Martin S J Effect of complete suprarenalectomy on oestral cycle of white rat with reference to suprarenal pituitary relationship Am J Physiol 100 180-191 (Mar) 1932
 - 29 Menkin V Effect of adrenal cortex extract on capillary permeability, Am J Physiol 129 691 697 (June) 1940
 - 30 Porges O Ueber Hypo-lykämie bei Morbus Addison sowie bei nebennierenlosen Hunden Ztschr f klin Med 69 341 349 1909
 - 31 Richter C P and Eckert, J F Mineral metabolism of adrenalectomized rats studied by appetite method Endocrinology 22 214 224 (Feb) 1938
 - 32 Rogoff J M and Stewart G V Studies on adrenal insufficiency, further blood studies (cholesterol and calcium) in control adrenalectomized dogs, Am J Physiol 86 25 31 (Aug) 1928
 - 33 Rokhsaz M Correlation of the endocrine glands I Interaction between the thyroid and

- Adrenal Diseases Baltimore Williams & Wilkins 1937 p 216
- 65 Truszkowski R and Zwemer H L Cortico adrenal insufficiency and potassium metabolism *Biochem J* 30 1345 1353 1936
 - 66 Valsalva A M Medical Essays and Observations Vol 2 p 315 1747
 - 67 Vaquez L H and Donzelot E Les crises d'hypertension artérielle paroxystique *Presse med* 34 1329 1331 (Oct) 1926
 - 68 Venning E H Conference on Metabolic Aspects of Convalescence, 10th Meeting June 15 16 New York Josiah Macy Jr Foundation 1945 p 197
 - 69 Voelcker A F Reports of the Medical Surgical and Pathological Registrars The Middlesex Hospital London Lewis 1894 1895
 - 70 Vulpian E F A Note sur les réactions propres au tissu des capsules surrénales chez les reptiles *Compt rend Soc biol* 2^e ser 3 223 224 1856
 - 71 Waterhouse R A case of suprarenal apoplexy *Lancet* 1 577 578 (Mar) 1911
 - 72 Whitcomb J C A chemical method for estimating epinephrine in blood *J Biol Chem* 108 633 643 (Mar) 1935
 - 73 Young H H Genital Abnormalities Hermaphroditism and Related Adrenal Diseases Baltimore Williams & Wilkins 1937
- ## II ANATOMY
- 1 Dietrich Koln A and Segmund Koln H *in* Handbuch der Speziellen pathologischen Anatomie und Histologie Vol 8 Berlin Springer 1926 pp 951 1071
 - 2 Gray H Anatomy of the Human Body ed 23 Philadelphia Lea & Febiger 1936 pp 1267 1270
 - 3 Scammon R E *in* Abts Pediatrics Philadelphia Saunders 1923 Vol 1 pp 374 376
 - 4 Schaeffer J P Morris Human Anatomy ed 10 Philadelphia Blakiston 1942 pp 1504 1507
 - 5 Selye H Textbook of Endocrinology Acta Endocrinologica Montreal Université de Montréal 1947 p 92
- ## III EMBRYOLOGY
- 1 Arey L H Developmental Anatomy ed 2 Philadelphia Saunders 1931 pp 407 408
 - 2 Keene M F L and Hewer E E Observations on the development of the human suprarenal gland *J Anat* 61 302 324 1927
 - 3 Zuckerkandl E *in* Manual of Human Embryology Philadelphia Lippincott 1912 Vol 2 pp 170 176
- ## IV CONGENITAL ANOMALIES
- 1 Busacchi P I corpi cromaffini del cuore umano *Arch ital anat embriol* 11 352 376 1912
 - 2 Kohn A Die Paraganglien *Arch f Mikr Anat* 62 263 365 1903
 - 3 Marchand Ueber accessorsche Nebennieren im Ligamentum latum *Arch f path Anat und Physiol* 92 11 19 (Apr) 1883
 - 4 Soffer L J Diseases of the Adrenals Philadelphia Lea & Febiger 1946 pp 12 13
 - 5 Thelander H E Congenital adrenal cortical insufficiency associated with macrogenitosomia follow up and terminal report *J Pediat* 29 213 221 (Aug) 1946
 - 6 Wiesel J Über accessorsche Nebennieren am Nebenhoden beim Menschen und über Compensations hypertrophie dieser Organe bei der Ratte Akademie der Wissenschaften (Sitzungsberichte der Mathematische Naturwissenschaftlichen classe) 108 (Abt 3) 257 280 (May) 1899
- ## V HISTOLOGY
- 1 Arnold J An investigation into the finer structure and the chemistry of the adrenal *Virchow's Arch Path Anat* 35 64 107 1866
 - 2 Cowdry E V A Textbook of Histology ed 2 Philadelphia Lea & Febiger 1938 pp 215 232
 - 3 Jordan H E A Textbook of Histology ed 8 New York Appleton 1930 pp 499 506
- ## VI FUNCTIONS
- ### A Gland as a Whole
- 1 Albright F Cushing's syndrome its pathological physiology its relation hip to the adreno genital syndrome and its connection with the problem of the reaction of the body to injurious agents (alarm reaction of Selye) *Harvey Lect* 38 123 186 1942 1943
 - 2 Britton W and Silvette H The Adrenal Cortex and Carbohydrate Metabolism *in* Cold Spring Harbor Symp on Quant Biol Cold Spring Harbor L I N Y 5 357 361 1937
 - 3 Cannon W B et al Some aspects of physiology of animals surviving complete exclusion of sympathetic nerve impulses *Am J Physiol* 89 84 107 (June) 1929
 - 4 Hartman F A and Thorn G W The biological method for the assay of cortin *Proc Soc. Exper Biol & Med* 28 94 95 (Nov) 1930
 - 5 Kendall E C The adrenal cortex *Arch Path* 32 474 501 (Sept) 1941
 - 6 Long C N H Katzin B and Fry E G Adrenal cortex and carbohydrate metabolism *Endocrinology* 25 309 344 (Feb) 1940
 - ✓ 7 Petersen W E Lactation *Physiol. Rev* 24 340 371 (July) 1944
 - 8 Thorn G W et al Medical progress studies on the relation of pituitary adrenal function to rheumatic disease *New England J Med* 241 529 537 (Oct) 1949
- ### B Individual Hormones
- 1 Abderhalden E and Gelhorn E Comparative effects of d and l adrenal on gas metabolism of organs under various conditions *Pflügers Arch ges Physiol* 212 523 534 1926
 - 2 Albright F Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 8th Meeting Oct 13 14 New York Josiah Macy Jr Foundation 1944 p 197
 - 3 Anrep A V The regulation of the coronary circulation *Physiol Rev* 6 596 629 (Oct) 1926
 - 4 Baumann J and Kurland S Changes in inorganic constituents of blood in suprarenal extomized cats and rabbits *J Biol Chem* 71 281 302 (Jan) 1927
 - 5 Boland E W and Headley N E Effects of cortisone acetate on rheumatoid arthritis *JAMA* 141 301 308 (Oct) 1949
 - 6 Boothby W M and Sandford J The calorigenic action of adrenalin chloride *Am J Physiol* 66 93 123 (Sept) 1923
 - 7 Britton S W and Silvette H Apparent prepotent function of adrenal glands *Am J Physiol* 100 701 713 (May) 1932
 - 8 — The Adrenal Cortex and Carbohydrate

- 9 Zondek H Diseases of the Endocrine Glands Baltimore Wood 1936 p 18
- G Miscellaneous Factors Influencing Adrenal Cortices
 - 1 Ingle D W A further study of the effect of diet on adrenal weights in rats *Endocrinology* 37 7 14 (July) 1945
 - 2 Selye H *Textbook of Endocrinology Acta Endocrinologica Montreal Universite de Mont real* 1947 p 135
 - 3 Tepperman J Engel F L and Long C N H Review of adrenal cortical hypertrophy *Endocrinology* 32 3 3-402 (May) 1943
- VII CHEMISTRY
 - 1 Aldrich T B Preliminary report on active principle of suprarenal gland *Am J Physiol* 5 437 461 (Aug) 1901
 - 2 Baqz Z S and Fischer P Nature de la substance sympathicomimetique extraite des nerfs ou des tissus des mammiferes *Arch internat de physiol* 35 3 91 (Aug) 1947
 - 3 Beall D Isolation of α -oestradiol and oestrone from horse testes *Biochem J* 34 1 93 1293 (Sept) 1940
 - 4 du Vigneaud V The significance of labile methyl groups in the diet and their relation to transmethylation *Harvey Lect* (1942 1943) 38 39 62 1943
 - 5 Goldenberg M Faber M Alston E J and Chargaff E C Evidence for the occurrence of nor epinephrine in the adrenal medulla *Science* 109 534 535 (May) 1949
 - 6 Goldenberg M Pines L L Baldwin E de F Greene H G and Roh C E The hemodynamic response of man to nor epinephrine and epinephrine and its relation to the problem of hypertension *Am J Med* 6 192 306 (Dec) 1948
 - 7 Grollman A *Essentials of Endocrinology* ed 2 Philadelphia Lippincott 1947 p 407
 - 8 Hartman F A and Brownell K A Hormone of adrenal cortex *Science* 72 6 (July) 1930
 - 9 Halton F Noradrenaline in adrenal medullary tumours *Nature* 163 217 (Feb) 1949
 - 10 Ingle D J Some studies on the role of the adrenal cortex in organic metabolism *Ann New York Acad Sc* 50 5 6 590 (June) 1949
 - 11 Kuzevica M H Chemistry and Physiology of Hormones *Am Assoc Advancement Sc Washington D C* 1944 p 57
 - 12 Osol A and Farrar G E The Dispensatory of the United States of America ed 24 Philadelphia Lippincott 1947 p 352
 - 13 *Ibid* pp 411 412
 - 14 *Ibid* p 1172
 - 15 Parkes A S Adrenal gonad relationship *Physiol Rev* 25 203 224 (Apr) 1945
 - 16 Selye H *Textbook of Endocrinology Acta Endocrinologica Montreal Universite de Montreal* 1947 pp 127 129
 - 17 Stolz F Über adrenalin und alkyl amino aceto benz Katerbin *Berlin chem Ges* 37 41 49 1904
 - 18 Svingen W W and Pfaffner J J Revival of rotomase adrenalectomized cats with an extract of suprarenal cortex *Science* 72 75 76 (July) 1930
 - 19 Taunter M L Tullar B F and Luduena F P *Levo arterenol Science* 107 39-40 (Jan) 1943
 - 20 Takamine J Adrenaline the active principle of the suprarenal glands and its mode of preparation *Am J Pharm* 73 523 531 1901
 - 21 von Euler U S and Liljestrand G Observations on pulmonary arterial blood pressure in cat *Acta physiol Scandinav* 12 301 3 11 1946
 - 22 Wells B H and Kendall E C Qualitative difference in effect of compounds separated from adrenal cortex on distribution of electrolytes and on atrophy of adrenal and thymus glands of rats *Proc Staff Meet., Mayo Clin* 51 133 139 (Feb) 1940
 - 23 West G B Quantitative studies of adrenaline and non adrenaline *J Physiol* 106 418-425 (Oct.) 1947
- VIII BIO ASSAY
 - 1 Barker J H, Eastland C J., and Evers N The colorimetric determination of adrenaline in suprarenal gland extracts *Biochem J* 26 2129 2143 1932
 - 2 Britton S W and Silvette H Some effects of cortico adrenal extract and other substances on adrenalectomized animals *Am. J Physiol* 99 15 32 (Dec) 1931
 - 3 Bulbring E Standardization of cortical extracts by use of drakes *J Physiol* 89 64 80 (Feb) 1937
 - 4 Cannon W B The emergency function of the medulla *Endocrinol & Metab* 2 1 1 1922
 - 5 Cannon W B and Hoxkins R G Effects of a phylla hypermoea and sensory stimulation on adrenal secretion *Am J Physiol* 29 274 2 9 1911
 - 6 Cartland G F., and Kuzevica M H Bioassay of adrenal cortical extracts direct comparison of rat and dog units *Am J Physiol* 117 6 8 635 (Dec.) 1936
 - 7 Dale H H and Laidlaw P P Significance of the adrenals in the action of certain alkaloids *J Physiol* 45 1 1912
 - 8 Dorfman R I The bioassay of adrenal cortical steroids *Ann New York Acad Sc* 50 556 574 (June) 1949
 - 9 Dorfman R I Ross E and Shipley R A Relative potencies of adrenal cortical steroids as determined by cold protection test and by glycogen deposition test *Endocrinology* 38 189 196 (Mar) 1946
 - 10 Dorfman R I Shipley R A Schaller S and Horvut H Studies on cold test as method for assay of adrenal cortical steroids *Endocrinology* 38 165 177 (Mar) 1946
 - 11 Eggleston N M Johnston B J and Dobner K Quantitative methods for bio-assay of glycoic activity of steroids and urinary extracts *Endocrinology* 38 197 211 (Mar) 1946
 - 12 Ehrmann H Die Wertbestimmung des Adrenalins in Blut *Arch exper Path* 111 97 111 1900
 - 13 Elliott, T R The control of the suprarenal glands by the planchic nerves *J Physiol* 44 3 4-409 1912
 - 14 Elmdjian F and Pincus G A stress-survival test for cortin *Endocrinology* 35 219 (Sept.) 1944 (Abstr)
 - 15 Evers J W R and DeFremercy P On a method of measuring fatigue in rats and its application for testing the suprarenal cortical hormone *Acta brev Neerland* 2 152 153 1932
 - 16 Eversole W J., Gaunt R. and Kendall E C Effect of adrenal steroids in water intoxica

- in man to administration of epinephrine *Am J Physiol* 121 325 330 (Feb) 1938
- 46 Knowlton A I, Loeb R N, Stoerk H C and Seegal H C Desoxycorticosterone acetate potentiation of its activity by sodium chloride *J Exper Med* 85 187 198 (Feb) 1947
 - 47 Kochakian C D Conference on Metabolic Aspects of Convalescence including Bone and Wound Healing 4th Meeting, June 11 12 New York Josiah Macy, Jr., Foundation 1943 p 166
 - 48 — Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 5th Meeting Oct 8 9 New York Josiah Macy Jr Foundation 1943 p 146
 - 49 Kuizenga M H, and Cartland G F Fractionation studies on adrenal cortex extract with notes on distribution of biological activity among crystalline and amorphous fractions *Endocrinology* 24 526 535 (Apr) 1939
 - 50 Lamson P D The effect of epinephrine and emotional stimuli on the red corpuscle content of the blood in rabbits *J Pharmacol Exper Therap* 8 167 171 1916
 - 51 Langley J N Observations on the physiological action of extracts of the suprarenal bodies *J Physiol* 27 237 256 1901
 - 52 Lieben S On the physiology of the tunica dartos *Pflügers Arch ges. & Physiol* 124 336 352 1908
 - 53 Loeb R F, Atchley D W, Benedict E M, and Leland J Electrolyte balance studies in adrenalectomized dogs with particular reference to excretion of sodium *J Exper Med* 57 775 792 (May) 1933
 - 54 Long C N H, Fry E G and Thompson A W Effect of adrenalectomy and adrenal cortical hormones upon pancreatic diabetes in the rat *Am J Physiol* 123 130-131 (July) 1938
 - 55 Long C N H, Katzin B and Fry F G Adrenal cortex and carbohydrate metabolism *Endocrinology* 26 309 344 (Feb) 1940
 - 56 Marine D and Baumann E J Duration of life after suprarenalectomy in cats and attempts to prolong it by injections of solutions containing sodium salts glucose and glycerol *Am J Physiol* 81 86 100 (June) 1927
 - 57 Marshall E K Jr and Davis D M The influence of the adrenals on the kidneys *J Pharmacol & Exper Therap* 8 525 550 1916
 - 58 Mason H L Chemistry of adrenal cortical hormone *Endocrinology* 25 405 412 (Sept) 1939
 - 59 McCullagh M P and Ryan E J Use of desoxycorticosterone acetate in Addison's disease *JAMA* 114 2530 2537 (June) 1940
 - 60 Moehlig R C and Jaffe I Syndrome simulating diabetes insipidus in dogs induced by desoxycorticosterone acetate clinical observation of syndrome with addition of tetany *J Lab & Clin Med* 27 1009 1012 (May) 1942
 - 61 Moore B and Furinton C O On the effects of complete removal of the suprarenal glands *Am J Physiol* 5 182 190 1901
 - 62 Nelson E E and Edmunds C W Some factors concerned in the polycythemia produced by epinephrine and physostigmine *J Pharmacol & Exper Therap* 23 154 155 (Mar) 1924
 - 63 Oliver G and Schafer E A The physiological effects of extracts of the suprarenal capsules *J Physiol* 18 230 276 1895
 - 64 Raab W Pathogenic significance of adrenal and related substances in heart muscle *Exper Med & Surg* 1 188 225 (May) 1943
 - 65 Ragan C, Ferricbe J W, Phyfe P, Atchley D W, and Loeb R F Syndrome of polydipsia and polyuria induced in normal animals by desoxycorticosterone acetate *Am J Physiol* 131 73 8 (Nov) 1940
 - 66 Recant L, Hume D M, Forsham P H and Thorn G W Studies on the effect of epinephrine on the pituitary-adrenocortical system *J Clin Endocrinol* 10 187 229 (Feb) 1950
 - 67 Schiffer F and Wertheimer E Leanness in adrenalectomized rats, *J Endocrinol* 5 147 151 (July) 1947
 - 68 Selye H and Hall C E Pathologic changes induced in various species by overdosage with desoxycorticosterone *Arch Path* 36 19 31 (July) 1943
 - 69 Sprague R G, Gastineau C F, Mason H L and Power M H Effects of synthetic 11 dehydrocorticosterone (compound A) in subject with Addison's disease *Am J Med* 4 175 185 (Feb) 1948
 - 70 Swanson E E Action of ephedrine pseudo ephedrine and epinephrine on bronchioles, *J Pharmacol Exper Therap* 36 541 568 (Aug) 1929
 - 71 Swingle W W, Parkins W M., and Remington J W Effect of desoxycorticosterone acetate and of blood serum transfusions upon circulation of adrenalectomized dog *Am J Physiol* 134 503 512 (Oct) 1941
 - 72 Swingle W W and Remington J W Role of adrenal cortex in physiological processes *Physiol Rev* 24 89 127 (Jan) 1944
 - 73 Tainter M L, Tullar B F., and Luduena F P *Levo arterenol Science* 107 39-40 (Jan) 1948
 - 74 Thorn G W The Diagnosis and Treatment of Adrenal Insufficiency Springfield Ill Thomas 1949 p 149
 - 75 *Ibid* p 154
 - 76 Thorn G W et al Medical progress studies on the relation of pituitary adrenal function to rheumatic disease *New England J Med* 241 579 537 (Oct) 1949
 - 77 Thorn G W, Dorrance M S and Day E Addison's disease evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients *Ann Int Med* 16 1053 1096 (June) 1942
 - 78 Thorn G W, Engel L L and Eisenberg H Effect of corticosterone and related compounds on renal excretion of electrolytes *J Exper Med* 68 161 171 (Aug) 1938
 - 79 Thorn G W, Engel L I and Lewis R A Effect of 17 hydroxy corticosterone and related adrenal cortical steroids on sodium and chloride excretion *Science* 94 348 349 (Oct) 1941
 - 80 Thorn G W., and Furor W M Desoxycorticosterone acetate therapy in Addison's disease clinical considerations *JAMA* 114 2517 2525 (June) 1940
 - 81 Vosburgh C H and Richards A N An experimental study of the sugar content and extravascular coagulation of blood after administration of adrenalin *J Physiol* 9 35 51 1903

- corticotrophic hormone J.A.M.A. 137 1005 1009 (July) 1948
- 54 Tournade A and Chabrol M L adrenalinémie Rev de méd 40 222 1923
 - 55 Trendelenburg P Bestimmung des Adrenalin gehaltes des Blutes Arch exper Path 63 161 1910
 - 56 Truszkowski R and Duszyńska J Protection of mice against potassium poisoning by corticoadrenal hormones Endocrinology 27 117 124 (July) 1940
 - 57 Ujderi E Assay of cortical hormone Endocrinology 23 871 876 (Dec) 1939
 - 58 Yennung H H Kazmin V E and Bell J C Biological assay of adrenal corticoids Endocrinology 38 73 83 (Feb) 1946
 - 59 von Euler U S Spectrophotometric determination of adrenalin in adrenal extracts Biochem Ztschr 260 18 25 1935
 - 60 Wada M and Kanowaka Z On the sensitivity of the denervated heart of non anesthetized non fastened dogs to adrenalin Toboku J Exper Med 27 9 19 (Aug) 1935
 - 61 West G B Some observations on effect of subcutaneous injections of suprarenal cortical hormone upon renal excretion of electrolytes by normal albino rats Quart J Pharm & Pharmacol 15 104 110 (Apr June) 1942
 - chromocytoma Brit J Surg 35 1:9 197 (Oct) 1947
 - 3 Broster L R Allen C Vines H W C Patterson J Greenwood A W Marrian G F and Butler G C The Adrenal Cortex Interscience London Chapman & Hall Ltd., 1938
 - 4 Cahill G F Hormonal tumors of adrenal Surgery 16 233 265 (Aug) 1944
 - 5 Duff H L and Bernstein C Five cases of Addison's disease with so called atrophy of adrenal cortex Bull Johns Hopkins Hosp 52 67 85 (Jan) 1933
 - 6 Guttman P H Addison's disease statistical analysis of 366 cases and study of the pathology Arch Path 10 42 45 (Nov) 1930
 - 7 Ness F C Tice G M Walker G A and Ockerblad N Adrenal tumor in female infant with hypertrichosis hypertension over development of external genitalia obesity but absence of breast enlargement J Clin Endocrinol 2 125 127 (Feb) 1942
 - 8 Parkes A S Adrenal gonad relationship Physiol Rev 25 25 254 (Apr) 1945
 - 9 Rowntree L H and Snell A M A Clinical Study of Addison's Disease Philadelphia Saunders 1931 p 317
 - 10 Selye H Textbook of Endocrinology Acta Endocrinologica Montreal Université de Montréal 1947 p 190
 - 11 Young H H Genital Abnormalities Hermaphroditism and Related Adrenal Diseases Baltimore Williams & Wilkins, 1937 pp 234 235
- ### IX PATHOLOGY
- 1 Burrows H Changes induced by oestrogens in adrenals of male mice J Path & Bact 43 125 126 (July) 1936
 - 2 Clausen H J Atrophy of adrenal cortex following administration of large amounts of progesterone Endocrinology 27 989 993 (Dec) 1940
 - 3 Dempsey E W Recent Progress in Hormone Research New York Acad Press 1948 Vol 3 pp 127 157
 - 4 Greep R O and Deane H W Cytochemical evidence for the cessation of hormone production in the zona glomerulosa of the rat's adrenal cortex after prolonged treatment with desoxycorticosterone acetate Endocrinology 40 417 425 (June) 1947
 - 5 Howard E and Gengradom M Effects of ovariectomy and administration of progesterone on adrenal x zone and uterus Endocrinology 26 1048 1052 (June) 1940
 - 6 Jones I C The relationship of the mouse adrenal cortex to the pituitary Endocrinology 45 514 536 (Nov) 1949
 - 7 Kameidori H J and Sodera W A L Changes induced in the adrenal cortical zones by ovarian hormones Endocrinology 41 21 26 (Jan) 1947
 - 8 Selye H Collip J H and Thomson D L Effect of oestrin on ovaries and adrenals Proc Soc Exper Biol & Med 32 1377 1381 (May) 1935
 - 9 Starkey W H and Schmidt M C H Jr Effect of testosterone propionate on x zone of mouse adrenal Endocrinology 23 339 344 (Sept) 1938
- ### X CLASSIFICATION
- 1 Barker N W Pathologic anatomy in 28 cases of Addison's disease Arch Path 8 432 450 (Sept) 1929
 - 2 Blacklock J W S Ferguson J W Mack W S Shafir J and Symington T Phaeochromocytoma Brit J Surg 35 1:9 197 (Oct) 1947
 - 3 Broster L R Allen C Vines H W C Patterson J Greenwood A W Marrian G F and Butler G C The Adrenal Cortex Interscience London Chapman & Hall Ltd., 1938
 - 4 Cahill G F Hormonal tumors of adrenal Surgery 16 233 265 (Aug) 1944
 - 5 Duff H L and Bernstein C Five cases of Addison's disease with so called atrophy of adrenal cortex Bull Johns Hopkins Hosp 52 67 85 (Jan) 1933
 - 6 Guttman P H Addison's disease statistical analysis of 366 cases and study of the pathology Arch Path 10 42 45 (Nov) 1930
 - 7 Ness F C Tice G M Walker G A and Ockerblad N Adrenal tumor in female infant with hypertrichosis hypertension over development of external genitalia obesity but absence of breast enlargement J Clin Endocrinol 2 125 127 (Feb) 1942
 - 8 Parkes A S Adrenal gonad relationship Physiol Rev 25 25 254 (Apr) 1945
 - 9 Rowntree L H and Snell A M A Clinical Study of Addison's Disease Philadelphia Saunders 1931 p 317
 - 10 Selye H Textbook of Endocrinology Acta Endocrinologica Montreal Université de Montréal 1947 p 190
 - 11 Young H H Genital Abnormalities Hermaphroditism and Related Adrenal Diseases Baltimore Williams & Wilkins, 1937 pp 234 235
- ### XIII EXAMINATION OF PATIENT
- 1 Armstrong C N and Simpson J Adrenal feminism due to carcinoma of adrenal cortex case report and review of literature Brit Med J 1 82 84 (Apr) 1943
 - 2 Bartels E C and Arnold W T Essential features for the diagnosis of pheochromocytoma report of a case Lahey Clin Bull 6 132 142 (July) 1949
 - 3 Bartels E C and Cattell M Pheochromocytoma its diagnosis and treatment Ann Surg 131 903 916 (June) 1950
 - 4 Bartels E C and Kingsley J W Diagnostic approach to pheochromocytoma report of a case Lahey Clin Bull 6 7 12 (July) 1948
 - 5 Becker M C Bass R D and Robbins C M Pheochromocytoma diagnosis and treatment Postgraduate Med 6 408-412 (Nov) 1949
 - 6 Blackwood James Presacral perineal pneumography Brit J Surg 154 111 118 (Sept) 1951
 - 7 Cutler H H Power M H and Wilder R M Concentrations of sodium chloride and potassium in blood plasma and urine of patients with Addison's disease their diagnostic significance Proc Staff Meet Mayo Clin 13 244 249 (Apr) 1938
 - 8 — Concentrations of chloride sodium and potassium in urine and blood their diagnostic significance in adrenal insufficiency J.A.M.A. 111 117 122 (July) 1938
 - 9 Drill V A Reactions from the use of benzodioxane (933F) in diagnosis of pheochromocytoma New England J Med 241 777 779 (Nov) 1949
 - 10 Engel A and von Euler U S Diagnostic value of increased output of noradrenaline and adrenaline in pheochromocytoma Lancet 2 387 (Sept) 1950

- the suprarenal cortex *Rev Irse endocrinol* 15 368 383 (Oct.) 1937
- 34 Roos A Assay of adrenal cortical extracts in adrenalectomized rats exposed to cold *Endocrinology* 33 26 281 (Nov.) 1943
 - 35 Russell J A Relationship of anterior pituitary and adrenal cortex in metabolism of carbohydrate *Am J Physiol* 128 552 561 (Feb.) 1940
 - 36 — Adrenals and hypophysis in carbohydrate metabolism of eviscerated rat *Am J Physiol* 140 98 106 (Oct.) 1943
 - 37 — Relationship of anterior pituitary to thyroid and adrenal cortex in control of carbohydrate metabolism in *Essays in Biology* 1943 p 509
 - 38 Schumacker H H and Fitor W M The interrelationship of the adrenal cortex and the anterior lobe of the hypophysis *Endocrinology* 18 676 692 (Nov Dec) 1934
 - 39 Selye H Textbook of Endocrinology Acta Endocrinologica Montreal Université de Montreal 1947 p 117
 - 40 Stein L and Wertheimer E Effect of adrenal ectomy on intestinal absorption involving osmotic work in rats *Proc Soc Exper Biol & Med* 46 172 174 (Jan.) 1941
 - 41 Swingle W W Parkins W M Taylor A R and Hays H W Study of circulatory failure of adrenal insufficiency and analogous shock like conditions *Am J Physiol* 123 659 667 (Sept.) 1948
 - 42 Swingle W W and Remington J W Role of adrenal cortex in physiological processes *Physiol Rev* 24 89 127 (Jan.) 1944
 - 43 Taylor N B and Caven W R Observations upon the serum calcium after adrenalectomy *Am J Physiol* 81 511 512 (July) 1927
 - 44 Zwemer R L and Lyons C Leucocyte changes after adrenal removal *Am J Physiol* 86 545 551 (Oct.) 1928
- ### D Hyperhormonal Effects
- 1 Abelin I and Althaus U On the antagonistic influence of the adrenal and thyroid hormones on glycogen metabolism of the liver *Helvet chim acta* 25 205 215 1942
 - 2 Aleschin B V and Sarenko P F The action of mediators on the thyroid gland *Am Rev Soviet Med* 4 269 270 (Feb.) 1947
 - 3 Black E M Hupper M and Rogers J The effects of adrenal feeding upon the iodine content of the thyroid gland *Am J Physiol* 59 222 226 (Feb.) 1927
 - 4 Cicconardi A and Lorusso G Influenza del corticosterone sulle modificazioni morfologiche del sangue periferico delle cavia trattate con la tiroxina *Boll soc ital biol sper* 20 63 65 1945
 - 5 Daoud A M and Gohar H A F The correlation between the action of insulin and adrenaline upon the muscle and liver glycogen *J Physiol* 80 314 322 (Dec.) 1933
 - 6 Koelsche G A and Kendall E C The relation of the suprarenal cortical hormone to nitrogen metabolism in experimental hyperthyroidism *Am J Physiol* 113 335 349 (Oct.) 1935
 - 7 Oehme C Antithyroid effect of adrenal cortex *Klin Wchnschr* 15 512 514 (Apr.) 1936
 - 8 Satzko K Augmented epinephrine secretion by insulin or peptone depends upon the integrity of the splanchnic nerves *Tohoku J Exper Med* 30 33 48 (Nov.) 1936
 - 9 Soffer L J Volterra A Gabriove J L Pollack A and Jacobs M Effect of iodine and adrenaline on thyrotropin in Graves disease and in normal and thyroidectomized dogs *Proc Soc Exper Biol & Med* 64 446 447 (Apr.) 1947
 - 10 Taylor N B and Caven W R Observations upon the serum calcium after adrenalectomy *Am J Physiol* 81 511 512 (July) 1927
- ### E Histophysiology
- 1 Albright F X teoporeosis *Ann Int Med* 6 861 882 (Dec.) 1947
 - 2 Blackman S S Jr Concerning the function and origin of the reticular zone of the adrenal cortex *Bull Johns Hopkins Hosp* 78 180-214 (Apr.) 1946
 - 3 Camber B Histochemical demonstration of ketosteroids in the adrenal cortex *Nature* 163 285 286 1949
 - 4 Deane H W and Greep R O Morphological and histochemical study of rat's adrenal cortex after hypophysectomy with comments on liver *Am J Anat* 79 117 145 (July) 1946
 - 5 Goldzieher M A and Hostet H Adrenal cortical hyperfunction, *Am J Surg* 27 93 106 (Jan.) 1935
 - 6 Greep R O and Deane H W The cytology and cytochemistry of the adrenal cortex *Ann New York Acad Sc* 50 596 645 (June) 1949
 - 7 — Cytochemical evidence for cessation of hormone production in zona glomerulosa of rat's adrenal cortex after prolonged treatment with desoxycorticosterone acetate *Endocrinology* 40 417 425 (June) 1947
 - 8 Knowlton A I Loeb E V Stoerk H C and Seegal B C Desoxycorticosterone acetate potentiation of its activity by odium chloride *J Exper Med* 85 187 198 (Feb.) 1947
- ### F Activity at Different Periods of Life
- 1 Hamilton H H and Hamilton J H Ageing in apparently normal men I Urinary titers of ketosteroids and of alpha hydroxy and beta hydroxy ketosteroids *J Clin Endocrinol* 8 433 452 (June) 1948
 - 2 Heard R D H The Hormones ed Pincus G and Thimmon H U New York Acad Press 1948 Vol 1 p 610
 - 3 Jaudon J C Further observations concerning hypofunction of adrenals during early life salt and water hormone deficiency *J Pediat* 32 641 669 (June) 1948
 - 4 McNeill M The adrenal of the newborn *Ulster Med J* 16 41 45 (May) 1947
 - 5 Provenzano R W Adrenocortical hypoplasia in the newborn infant *New England J Med* 242 87 (Jan.) 1950
 - 6 Venning E H Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 10th Meeting June 15 16 New York Josiah Macy Jr Foundation 1945 p 197
 - 7 — The effect of ACTH during the neonatal period *Proc of the First Clinical ACTH Conference Philadelphia Blackiston* 1950 pp 25 31
 - 8 Venning E Randall J P and Gyorgy P Excretion of glucorticoids in the newborn *Endocrinology* 45 430-434 (Apr.) 1949



FIG 268 ADRENAL GLAND Normal adult adrenal gland The different zones are not well demarcated Zona fasciculata is easily recognized by the longitudinal arrangement of darker staining cells Zona reticularis and medulla fuse into one another ($\times 29$)

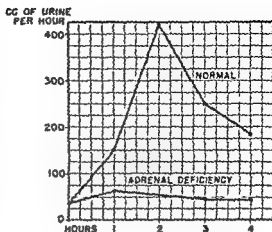


CHART 87 ADRENAL WATER TEST The chart illustrates diuresis in a normal individual (peaked curve) after ingestion of water as compared with water retention in a case of Addison's disease (flat curve) Nine cc of water/1 lb of body weight was given 1 hr before first specimen was collected

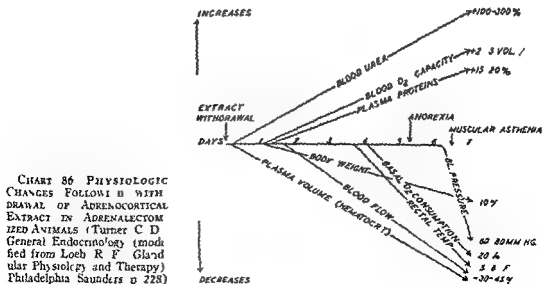


CHART 86 PHYSIOLOGIC CHANGES FOLLOWING WITHDRAWAL OF ADRENOCORTICAL EXTRACT IN ADRENALECTOMIZED ANIMALS (Turner C D General Endocrinology (modified from Loeb R F Glandular Physiology and Therapy) Philadelphia Saunders p 228)

- tion *Am J Physiol* 135 378 382 (Jan) 1941
- 17 Folin O, Cannon W H and Denis W A new colorimetric method for the determination of epinephrine *J Biol Chem* 13 477 483 1913
 - 18 Gaarenstroom J H Waterman L and Laqueur L A method for standardizing the cortical hormone *Acta brev Neerland* 7 10 13 1937
 - 19 Gasser H E and Meek W J A study of the mechanisms by which muscular exercise produces acceleration of the heart *Am J Physiol* 34 48 71 1914
 - 20 Goldenberg N Faber M Alston E J and Chargoif E C Evidence for the occurrence of nor epinephrine in the adrenal medulla *Science* 109 534 535 (May) 1949
 - 21 Grattan J F and Jensen H Effect of pituitary adrenocorticotrophic hormone and of various adrenal cortical principles on insulin hypoglycemia and liver glycogen *J Biol Chem* 135 511 517 (Sept) 1940
 - 22 Grollman A Biological assay of adrenal cortical activity *Endocrinology* 29 855 861 (Dec) 1941
 - 23 Grollman A and Firor W M Studies on adrenal preparation of active extract of hormone of adrenal cortex *J Biol Chem* 100 429 439 (Apr) 1933
 - 24 Harrop G A Jr Pfiffner J J Weinstein A and Swingle W W Biological method of assay of adrenal cortical hormone *Proc Soc Exper Biol & Med* 29 449 451 (Jan) 1932
 - 25 Hartman F A Brownell K A and Crosby A A Relation of cortin to maintenance of body temperature *Am J Physiol* 98 674 686 (Nov) 1931
 - 26 Hartman F A Lewis L A and Thatcher J S Assay of sodium retaining substances *Proc Soc Exper Biol & Med* 48 60 64 (Oct) 1941
 - 27 Hartman F A McCordock A and Loder M M Conditions determining adrenal secretion *Am J Physiol* 64 1 34 (Mar) 1923
 - 28 Hartman F A and Thorn G W Biological method for assay of cortin *Proc Soc Exper Biol & Med* 28 94 95 (Nov) 1930
 - 29 Hunter G and Cantor M M Adrenal cortical hormone method of assay and of preparation *Canad M A J* 37 368 377 (Oct) 1937
 - 30 Hyman C and Chambers R Effect of adrenal cortical compounds on edema formation of frogs hind limbs *Endocrinology* 32 310 318 (Apr) 1943
 - 31 Ingle D J Work capacity of adrenalectomized rat treated with cortin *Am J Physiol* 116 622 625 (Aug) 1936
 - 32 — Quantitative assay of adrenal cortical hormones by muscle work test in adrenalectomized nephrectomized rat *Endocrinology* 34 191 202 (Mar) 1944
 - 33 Ingle D J and Kendall E C Influence of amorphous fraction from adrenal cortex on efficiency of muscle *Proc Soc Exper Biol & Med* 45 602 606 (Nov) 1940
 - 34 Jensen H and Grattan J F Identity of glycotrophic (anti insulin) substance of anterior pituitary gland *Am J Physiol* 128 270 275 (Jan) 1940
 - 35 Kendall E C Hormones of adrenal cortex *Endocrinology* 30 853 860 (June) 1942
 - 36 Kutz R L Method of assay of extracts containing suprarenal cortical hormone, *Proc Soc Exper Biol & Med* 29 91 93 (Oct) 1931
 - 37 Lawen A Quantitative Untersuchungen über die Gefasswirkung von Suprarenin *Arch f Exper Path* 51 415 441 (July) 1904
 - 38 Lewis L A and Page I H Method of assaying adrenal preparations for protective action against toxic material (typhoid vaccine) *Fed Proc* 5 63 (Feb) 1946
 - 39 Mercier J A new colorimetric method for determination of adrenaline comparison with biological assay in dog *Compt rend Soc Biol* 138 935 936 (Nov) 1944
 - 40 Olson R E Jacobs F A Richard D Thayer S A Kopp L J and Wade N J Comparative bioassay of several extracts of adrenal cortex in tests employing 4 separate physiological responses *Endocrinology* 35 430-455 (Dec) 1944
 - 41 Olson H E Thayer S A and Kopp L J Glycogenic activity of certain crystalline steroids of adrenal cortex when administered singly and with cortical extract to fasted normal and adrenalectomized rats *Endocrinology* 35 464 472 (Dec) 1944
 - 42 Pabst M L Sheppard R and Kuzeaga M H Comparison of liver glycogen deposition and work performance tests for bio assay of adrenal cortex hormones *Endocrinology* 41 55 65 (July) 1947
 - 43 Palmer G H and Joseph G H Capillary permeability perfusion of frog and guinea pig hind limbs *Am J Physiol* 146 126 132 (Apr) 1946
 - 44 Perla D and Gottesman J M Injections of cortin on resistance of suprarenalectomized rats biological assay of extracts of suprarenal cortex *Proc Soc Exper Biol & Med* 28 475 477 (Feb) 1931
 - 45 — Effect of injections of cortin on resistance of suprarenalectomized rats to histamine poisoning *Proc Soc Exper Biol & Med* 28 650 653 (Mar) 1931
 - 46 Pfiffner J J Swingle W W and Vars H M Cortical hormone requirement of adrenalectomized dog with special reference to method of assay, *J Biol Chem* 104 101 116 (Mar) 1934
 - 47 Reinecke R M and Kendall E C Method for bio assay of hormones of adrenal cortex which influence deposition of glycogen in liver *Endocrinology* 31 573 577 (Dec) 1942
 - 48 Rogoff J M The adrenal medulla *J A MA* 104 2088 1935
 - 49 Roos A Assay of adrenal cortical extracts in adrenalectomized rats exposed to cold *Endocrinology* 33 76 81 (Nov) 1943
 - 50 Selye H and Schenker V Rapid and sensitive method for bioassay of adrenal cortical hormone *Proc Soc Exper Biol & Med* 39 518 522 (Dec) 1938
 - 51 Sugawara T Comparison of cat paradoxical eye reaction and rabbit intestine strip method for assay of epinephrine content of blood of cat *Tohoku J Exper Med* 8 355 404 (Apr) 1927
 - 52 Thompson R E Biological assay of epinephrine *J Am Pharm A* 34 265 269 (Oct) 1945
 - 53 Thorn G W Forsham P H Prunty F T G and Hills A G Test for adrenal cortical sufficiency the response to pituitary adreno

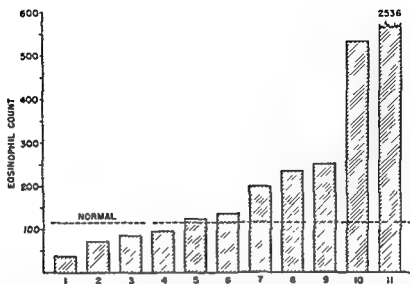


CHART 89 TOTAL EOSINOPHIL COUNTS IN VARIOUS ENDOCRINOLOGIC AND SYSTEMIC DISORDERS The broken line is the average of 180 separate total eosinophil counts taken on different blood samples from 16 normal females

NO	TYPES OF CASES	CASES	RANGE
1	Cushing's syndrome	4	0-100
2	Hirsutism obesity abdominal striae hypertension or mild virilism	13	0-14
3	Gonadal disturbances		
	Ovarian agenesis	4	38-250
	Hypergonadotropic type with tubular failure	1	
	Precocious puberty	1	
4	Enlarged sella turcica	7	0-181
5	Acromegaly	4	18-187
6	Myxedema	4	20-250
7	Addison's disease	1	260
8	Pituitary insufficiency		182-462
	Simmonds type	3	
	Sheehan's type	2	
9	Rheumatoid arthritis	3	68-681
10	Hypopituitary conditions		400-683
	Pituitary dwarf	2	
	Postoperative pituitary tumor	2	
11	Atopic dermatitis	2	1919-4731

The average for these was 2536 and is included to show high total eosinophil count in a disease in which eosinophilia is a characteristic finding

A larger experience has demonstrated that the level of circulating eosinophils is diagnostically unreliable in any one case

- 11 Godfrey J. Pheochromocytoma in diabetes. Abstract of paper at Clinical Meeting of N E Diabetes Assoc. Hanover, N H. Feb 9 1949
- 12 Goldenberg M and Aranow, H. Diagnosis of pheochromocytoma by the adrenergic blocking action of benzodioxan. *JAMA* 143 1139 1143 (July) 1950
- 13 Grimson K S Longino F H, Kernodle C E and O'Rear H H. Treatment of a patient with pheochromocytoma. *JAMA* 140 1273 1274 (Aug) 1949
- 14 Guarneri V and Evans J A. Pheochromocytoma: report of a case with a new diagnostic test. *Am J Med* 4 806 813 (June) 1948
- 15 Hills A G Forsham P H and Finch C A. Changes in circulating leukocytes induced by the administration of pituitary adrenocorticotrophic hormone (ACTH) in man. *Blood* 3 755 768 (July) 1948
- 16 Hines E A and Brown G E. A standard stimulus for measuring vasomotor reactions: its application in the study of hypertension. *Proc Staff Meet Mayo Clin* 1 332 335 (June) 1932
- 17 Hurxthal L M. Technic of testosterone pellet implantation by abdominal trocar. *S Clin North America* 22 793 794 (June) 1942
- 18 —. Unpublished data.
- 19 Kepler E J and Mason H L. Relation of urinary steroids to diagnosis of adrenal cortical tumors and adrenal cortical hyperplasia: quantitative and isolation studies. *J Clin Endocrinol* 7 543 558 (Aug) 1947
- 20 La Due J S Murison P J and Pack G T. Use of tertialthylammonium bromide as a diagnostic test for pheochromocytoma. *Ann Int Med* 29 914 921 (Nov) 1948
- 21 Levy M S Power M H and Kepler E J. Specificity of water test as diagnostic procedure in Addison's disease. *J Clin Endocrinol* 6 607 632 (Sept) 1946
- 22 Mauer H C. Intrathoracic pheochromocytoma. *Ann Surg* 130 1059 1065 (Dec) 1949
- 23 Maycock R L and Rose E. Insensitivity to epinephrine in a patient with a functioning tumor of the adrenal medulla. *Am J Med Sc* 213 324 330 (Mar) 1947
- 24 Roth H M and Kvale W F. Tentative test for pheochromocytoma. *Am J Med Sc* 210 653 660 (Nov) 1945
- 25 —. Pharmacologic tests as an aid in diagnosis of pheochromocytoma: modern concepts of cardiovascular disease. *Am Heart Assn* 18 41 42 (May) 1949
- 26 Spear H C and Griswold D. The use of dibenamine in pheochromocytoma. *New England J Med* 239 736 739 (Nov) 1948
- 27 Taliaferro I Adams R A and Haag H B. Benzodioxan test. *JAMA* 140 1271 1273 (Aug) 1949
- 28 Thorn G T. The Diagnosis and Treatment of Adrenal Insufficiency. Springfield Ill: Thomas 1949 p 54
- 29 Thorn G W Forsham P H Prunty F T G and Hills A G. Test for adrenal cortical insufficiency. The response to pituitary adrenocorticotrophic hormone. *JAMA* 137 1005 1009 (July) 1948
- 30 Truszkowski R and Zwemer R L. Determination of blood potassium. *Biochem J* 31 229 233 (Feb) 1937
- 31 Wilburne M Katz L N Rodbard S and Surtshin A. The action of N N dibenzyl beta chloroethylamine dibenamine in hypertensive dogs. *J Pharm & Exper Therap* 90 215 223 (July) 1947

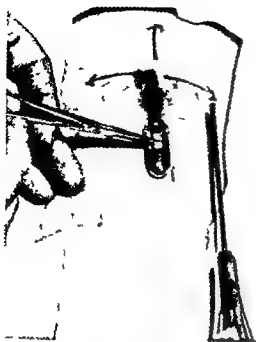


FIG 269 PELLET IMPLANTATION WITH TROCAR. The pellet is being inserted. The rod by which it is pushed in is shown at right. The arrows indicate the direction in which other pellets are to be implanted.

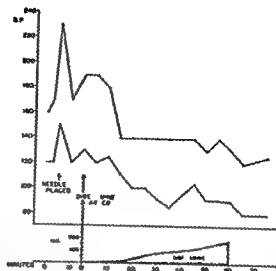


CHART 91 DIBENAMINE TEST IN PHEOCHROMOCYTOMA. Dibenamine was cautiously introduced in the vein. BP fell to a level lower than has been noted previously due to persistent hypertension (see also Chart 91) (Bartels E. C. and Cattell T. Pheochromocytoma: its diagnosis and treatment. *Ann Surg* 131:903-916).

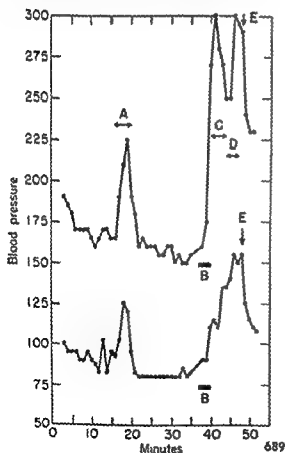


CHART 93 SEVERE REACTION TO BENZODIOXANE IN HYPERTENSION. (A) Spontaneous rise in BP producing precordial pain. (B) Injection of benzodioxane by rise in blood pressure, light-headedness, vertigo and severe precordial pain. (Drill V. A. Reactions from use of benzodioxane (933 F) in diagnosis of pheochromocytoma. *New England J. Med.* 241:777-779).

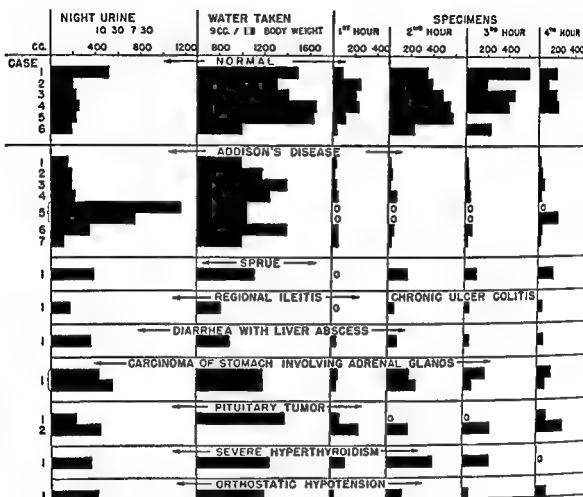


CHART 88 ADRENAL WATER IN VARIOUS DISEASES Part I of the test and the water excretion each hour after ingestion of water (Bartels)

	face knuckles nipples axillae, penis, scrotum labia anal region bluish black freckles are very characteristic all mucous membranes and ocular fundi may show patchy bluish black discolorations nails may have pigment spots or longitudinal bands ■ vitiligo present in 1 to 20 per cent ¹⁰⁰ reported in Negroes (see Figs 271 273, 275) ¹⁰ Over 98 per cent of cases have bronzing of the skin
e Color	
2 Hair	
a Head	Normal
b Facial	Normal
■ Axillary	Regrows slowly after shaving occasionally absent
d Pubic	Normal decreased or, rarely absent (see Fig 274)
■ Body	Normal
F HEAD	
1 Shape and size	Normal
2 Facial expression	Often languid listless dull
3 Eyes	
a General	Normal conjunctivae and sclerae may be pigmented
b Fundi	Normal or may show pigment
c Visual	
(1) Fields	Normal
(2) Acuity	Normal
4 Ears and nose	Normal hearing may be decreased
5 Mouth and throat	
a General	Not remarkable bluish black pigmentation of mucous membranes and tongue
■ Teeth	Normal tend to have apical abscesses and poor gums
c Larynx (voice)	May be weak on account of general muscular atonia
G NECK	
1 General	Normal typical pigmentation may be found
2 Thyroid	Normal
H CHEST	Normal or signs of healed or active tuberculosis
I HEART AND PERIPHERAL VESSELS	
1 Heart	Small sounds may be faint and distant
2 Rate and rhythm	Normal or tachycardia
3 Blood pressure	Depends on level before onset of disease but usually reduced low or unobtainable in acute crisis average systolic 80 to 100 mm and diastolic 50 to 70 mm ²⁰
4 Peripheral arteries and veins	Soft thin or not palpable erect posture may aggravate hypotension and increase pulse rate resulting in syncope (see 40 XIV F)
5 Vasomotor	Loss of tone presumably no flushing
J BREASTS	
1 Male	Normal occasionally ■ gynecomastia ^{6, 77} increased pigmentation of areolae
2 Female	Loss of fat areolae are darker than normal
K ABDOMEN	
1 Liver	Normal
2 Spleen	May be palpable
3 Hernia	None
4 Tumor	None as a rule

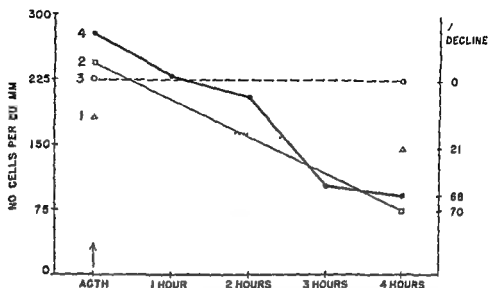


CHART 90 TOTAL CIRCULATING EOSINOPHILS PER CU MM BEFORE AND AFTER INTRAMUSCULAR INJECTION OF ACTH (1) Age 30 normal male Without injection of ACTH (not fasting on first count) (2) Normal obese young woman after injection of 30 mg of ACTH A normal response ■ shown by a 10% decline in total eosinophilic count (3) Counts on blood withdrawn before injection of ACTH and again after 4 hrs incubation (Patient 2) Note no change in count (4) Age 28 male with Reiter's syndrome Results after 60 mg of ACTH Normal response 68% decline in the total number of eosinophils

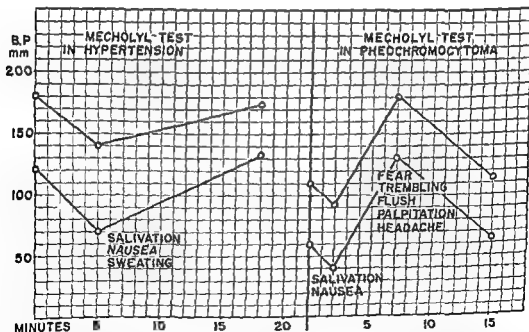


CHART 91 MECHOLYL TEST The chart shows the effect of mecholyl on BP in a hypertensive patient as compared with one with pheochromocytoma. In the cases tested so far the injection of mecholyl has been followed by a rise in pressure as illustrated. A similar provocative action may be obtained by the use of histamine and tetraethylammonium bromide. Negative responses do not always exclude pheochromocytoma (Guarnieri V and Evans J A Pheochromocytoma report of case with new diagnostic test Am J Med 4 806 813)

4 Uric acid	Normal or increased in crisis
5 Cholesterol	Variable usually low
6 Sodium	Variable depending on chloride level decreased in crisis
7 Potassium	Normal or increased in crisis
8 Calcium	Normal or increased ^{16 41 60}
9 Phosphorus	Normal or slightly increased ^{16 41 60}
10 Phosphatase	Normal
11 Chlorides	Variable, depending on sodium level but may be independent of potassium values usually decreased in crisis ⁹
12 Iodine	Normal ²
13 Creatine	Normal or increased ⁴²
14 Magnesium	Normal ¹⁶ or increased ⁶⁰
15 Bilirubin	Normal ¹⁰³
16 Bicarbonate	Normal may go down with chlorides during crisis
17 Carbon dioxide combining power	Normal or decreased ^{60 61}
18 Vitamin C	Low ⁴³

D FUNCTION TESTS

1 Tolerance	
a Glucose	
(1) Oral	Low curve with venous blood normal curve with capillary blood, if absorption is adequate (see Table 102, p 1426 103 113 a) ⁶⁸
(2) Intravenous	Normal curve ⁹
b Glucose insulin	Flat curve
■ Insulin	Normal or marked prolongation of hypoglycemic response
2 Adrenal water	Positive ⁷
3 Salt deprivation	Positive ⁷
4 Balance	
a Nitrogen	Negative often
5 Renal	
a Phenolsulfonphthalein	Normal or decreased ⁶⁰
b Clearance	
(1) Urea	Normal or decreased
(2) Creatinine	Decreased ⁶¹
(3) Inulin	Decreased ⁶⁰
6 Liver	
a Bromosulphthalein	Impaired
b Hippuric acid (IV)	Below normal ¹⁰⁰
7 ACTH	Positive (see 39 VIII 4 5 c) ^{11 60 70 124}

E MISCELLANEOUS TESTS

1 Basal metabolic rate	Moderately low average minus 15 to minus 20 per cent ^{8 4}
2 Circulation time	No data probably decreased
3 Sedimentation rate	Increased usually
4 Specific dynamic action of protein	No data
5 Gastric analysis	Achlorhydria common free hydrochloric acid is reduced
6 Electrocardiogram	No typical changes ^{11 30 101 1} low isoelectric or diaphasic T waves in all leads T ₁ T ₂ inverted occasionally and T ₃ T ₄ frequently ST interval may be prolonged

SECTION 40

ADDISON'S DISEASE

- I DEFINITION** A condition resulting from almost complete destruction of the adrenal cortices and characterized in general by asthenia, weight loss, low blood pressure, gastro intestinal symptoms and often pigmentation of skin and mucous membranes, acute or chronic types may occur
- II APPEARANCE** Thin, often with localized areas of pigmentation and lacking the bloom of health, severe or acute cases look very ill, languorous and their prostration may be quite marked (see Figs 270 and 271)
- III AGE** Any age, chiefly 20 to 40 years, youngest reported at 6½ months^{10-18 104 105}
- IV SEX** About equal, slight male predominance¹⁰²
- V MENTAL DEVIATIONS**
- A INTELLIGENCE** Normal variations
- B RESPONSIVENESS** May be impaired because of exhausting nature of disease
- C OTHER ABNORMALITIES** Irritability depression, delirium, coma
- VI PHYSICAL STATUS**
- A NUTRITION** Rarely cachexia
- 1 Weight** Below average all lose some—about 20 to 30 lbs is common
- 2 Fat distribution** Little or no fat deposits
- B STATURE** Normal even when disease develops in childhood decreased height age¹⁰⁴
- C EXTREMITIES**
- 1 Upper** Normal elbows may have a grayish silver appearance
- a Hands** Normal
- b Fingers** Normal knuckles, nail beds and creases of palms may be pigmented
- c Span** Normal
- 2 Lower** Normal knees may be pigmented
- a Feet** Normal
- b Toes** Normal
- D SPINE** Normal
- E INTEGUMENT**
- 1 General** Maintains elasticity normal amount of moisture but changes in electrolytic content (see 40 VI D)
- a Texture** Normal desquamation has been reported
- b Temperature** Subnormal if no infection may be elevated with carcinoma of adrenals¹⁸
- c Eruptions** None
- d Pigmentation** No change or else various shades of darkening, from light tan to burnt umber most prominent in exposed areas, scars or parts subjected to friction, as elbows neck,

IX ETIOLOGY

A. PRIMARY CAUSES^{20, 23, 122}

- 1 Tuberculosis (69.7%) (seldom primary)

TABLE 50 RELATION TO TUBERCULOSIS*

	NUMBER OF CASES
Previous history of tuberculosis with recovery	31
Tuberculosis (all active) before onset of Addison's disease	26
No history of tuberculosis	27

* Lungs, bones, glands, kidneys

TABLE 51 CLINICAL EVIDENCE OF TUBERCULOSIS ELSEWHERE

	NUMBER OF CASES
Pulmonary	60
No evidence	31
Questionable	10
Elsewhere	
Bone	34
Lymph nodes etc	7
Genito-urinary tract	4
Gastro-intestinal tract	1

TABLE 52 FIFTY-ONE CASES WITH TUBERCULOSIS OF ADRENALS

INVOLVEMENT	FINDINGS	NUMBER OF CASES
Unilateral	No symptoms	15*
Bilateral	Clinical signs	25
Bilateral	Latent	6
Bilateral	Undiagnosed	5

* It is probable that evidence of adrenal insufficiency might be obtained in more of these cases today

- 2 Idiopathic atrophy (16.1%) — Many factors have been considered as acute or chronic diseases but cause still remains obscure
- 3 Amyloid disease (1.7%)
- 4 Hemochromatosis
- 5 Tumor (1.7%) (see Protocol 40 XXXI)
 - a Malignant destruction
 - b Pressure atrophy
- 6 Venous thrombosis (0.7%)
- 7 Embolism (0.2%)
- 8 Syphilis (0.2%)
- 9 Pituitary hypofunction (see 7)

- 10 Removal of adrenal tumor with absent or atrophic gland on other side
- 11 Torulosis or histoplasmosis²²
- 12 Scleroderma
- 13 Meningococcus—see 41 III A 2¹⁰⁸

B. SECONDARY CAUSES

- 1 Pheochromocytoma
- 2 Carcinoma of cortex
- 3 Metastatic cancer especially of lungs⁹
- 4 Removal of sufficient adrenal tissue

X PATHOLOGY

A. GROSS

- 1 Adrenal glands^{1, 9, 26, 34, 1, 71, 8, 92}

- a Atrophy—primary contracted adrenal (3 of 19 autopsied cases at Lahey Clinic)

(1) Size

- (a) Very small, difficult to find
- (b) Weight—0.75 to 3 Gm

(2) Color—gray to brownish red

- (3) Surface—smooth often resembling cirrhotic liver

(4) Cortex—thin

(5) Medulla

- (a) Normal

- (b) Reduced

(6) Both glands involved

- b Hypoplasia—small size

- c Tuberculosis (15 of 19 autopsied cases at Lahey Clinic or 79%)

- (1) Size—often enlarged, about 22 to 28 Gm

(2) Color

- (a) Yellow
- (b) Yellowish gray
- (c) Reddish gray

(3) Capsule

- (a) Thickened
- (b) Adherent

(4) Consistency—rubbery

- (5) Cortex and medulla may be destroyed

- (a) Completely

- (b) Partially

- (6) Caseation with abscess (see Fig 277)

(7) Calcified areas

(8) Hemorrhage

- (9) Process may be

- (a) Acute

- (b) Chronic

- (c) Combination of both

L GENITALIA

1 Male

- a Penis Normal, may be pigmented
- b Testes Normal
- c Prostate Normal or atrophied⁶⁷

2 Female

- a External Normal, outer margin of labia may be pigmented
- b Internal Normal

M NEUROMUSCULAR

- 1 Muscles Weakness, loss of tone
- 2 Gait As might be expected with varying degree of weakness
- 3 Body movements Not remarkable, other than listless
- 4 Tremor None
- 5 Paresthesias None
- 6 Reflexes Normal

N SPEECH

As with severe asthenia, occasionally slurred

VII LABORATORY DATA

A URINE

- 1 General Decreased output specific gravity often high, other changes due to local kidney disease as - tuberculosis, pyelonephritis or nephrosis
- 2 Special analyses
 - a Sugar Absent or present only with associated diabetes mellitus
 - b Albumin May be found
 - c Nitrogen Normal
 - d Creatine Normal or increased⁸⁸
 - e Creatinine Normal
 - f Sodium Increased until body depletion occurs
 - g Potassium Decreased
 - h Calcium Normal
 - i Phosphorus Normal
 - j Chlorides Increased until body depletion occurs
 - k Iodine Normal

B HEMATOLOGY⁸

- 1 Red blood cells Decreased slightly (rarely below 3 million) or increased with hemoconcentration
- 2 Hemoglobin Decreased or increased with hemoconcentration
- 3 White blood cells Normal or slightly below, little rise with infection¹¹
- 4 Differential Relative lymphocytosis except with infection when percentage may drop eosinophils (total) average 322/cu mm¹¹²
- 5 Hematocrit Normal or increased during crisis

C BLOOD CHEMICAL ANALYSES (abnormal changes develop chiefly during a crisis or impending crisis)

- 1 Sugar Normal or low (true diabetes may be present)^{11 98}
- 2 Nonprotein nitrogen Normal or increased⁹
- 3 Protein Normal or increased with hemoconcentration in crisis
 - a Albumin Normal or decreased^{23 41 63}
 - b Globulin Normal or increased^{3 41 63}
 - c A/G ratio Normal or decreased^{16, 41 85}
 - d Fibrinogen Normal or increased⁶⁵

IX ETIOLOGY

A PRIMARY CAUSES^{38 53 122}

- 1 Tuberculosis (69.7%) (seldom primary)

TABLE 50 RELATION TO TUBERCULOSIS*

	NUMBER OF CASES
Previous history of tuberculosis with recovery	31
Tuberculosis (still active) before onset of Addison's disease	26
No history of tuberculosis	27

* Lungs, bones, glands, kidneys

TABLE 51 CLINICAL EVIDENCE OF TUBERCULOSIS ELSEWHERE

	NUMBER OF CASES
Pulmonary	60
No evidence	31
Questionable	10
Elsewhere	
Bone	34
Lymph nodes etc	7
Genito urinary tract	4
Gastro intestinal tract	1

TABLE 52 FIFTY ONE CASES WITH TUBERCULOSIS OF ADRENALS

INVOLVEMENT	FINDINGS	NUMBER OF CASES
Unilateral	No symptoms	15*
Bilateral	Clinical signs	25
Bilateral	Latent	6
Bilateral	Undiagnosed	5

* It is probable that evidence of adrenal insufficiency might be obtained in more of these cases today

- 2 Idiopathic atrophy (16.1%) — Many factors have been considered as acute or chronic diseases but cause still remains obscure
- 3 Amyloid disease (1.7%)
- 4 Hemochromatosis
- 5 Tumor (1.7%) (see Protocol 40 XXXI)
 - a Malignant destruction
 - b Pressure atrophy
- 6 Venous thrombosis (0.7%)
- 7 Embolism (0.2%)
- 8 Syphilis (0.2%)
- 9 Pituitary hypofunction (see 7)

- 10 Removal of adrenal tumor with absent or atrophic gland on other side
- 11 Torulosis or histoplasmosis⁷⁹
- 12 Scleroderma
- 13 Meningococcus—see 41 III A 2¹⁰⁶

B SECONDARY CAUSES

- 1 Pheochromocytoma
- 2 Carcinoma of cortex
- 3 Metastatic cancer, especially of lungs⁹
- 4 Removal of sufficient adrenal tissue

X PATHOLOGY

1 GROSS

- 1 Adrenal glands^{1 9 20 36 1 1 8, 92}

- a Atrophy—primary contracted adrenal (3 of 19 autopsied cases at Lahey Clinic)

(1) Size

- (a) Very small difficult to find
- (b) Weight—0.75 to 3 Gm

(2) Color—gray to brownish red

- (3) Surface—smooth, often resembling cirrhotic liver

(4) Cortex—thin

(5) Medulla

- (a) Normal
- (b) Reduced

(6) Both glands involved

- b Hypoplasia—small size

- c Tuberculosis (15 of 19 autopsied cases at Lahey Clinic or 79%)

- (1) Size—often enlarged, about 22 to 28 Gm

(2) Color

- (a) Yellow
- (b) Yellowish gray
- (c) Reddish gray

(3) Capsule

- (a) Thickened
- (b) Adherent

(4) Consistency—rubbery

- (5) Cortex and medulla may be destroyed

- (a) Completely
- (b) Partially

(6) Caseation with abscess (see Fig 277)

(7) Calcified areas

(8) Hemorrhage

(9) Process may be

- (a) Acute
- (b) Chronic
- (c) Combination of both

	low complexes, pattern may revert to normal or further signs of myocardial damage may develop, due to an increase in heart size with therapy ⁴³
7 Blood volume	Normal or decreased in crisis
8 pH	No data
9 Total base	Normal or decreased in crisis
10 Spinal fluid	No data
11 Fecal excretion	No data
12 Electro encephalogram	Slower alpha rhythm and frontal preponderance than normal, absence or decreased number of low voltage, fast frequency (beta) waves, sensitivity to hyperventilation is increased, about 70 per cent have abnormal findings ⁴⁸
F URINARY HORMONE ASSAYS	
1 FSH	Normal ^{7 64 64 67 87}
2 LH	No data
3 Estrogens	Normal (also in pregnancy) ^{64 7- 87}
4 Pregnanediol	May be present premenstrually or continuously if DOCA is administered normal in pregnancy ^{4 87}
5 17 ketosteroids	Low, about 1 to 4 mg /24 hrs in females about 1 to 9 mg /24 hrs in males ^{11 7 44 62 67 8- 87 100 113 114}
6 11 oxysteroids	Low or absent ^{22 31 10 131 13}
7 Aschheim Zondek	No data
8 TSH	No data
G BIOPSY	
1 Endometrial	Normal, if regular catamenia
2 Testicular	Atrophic changes possible, but usually normal ^{19 111}
H VAGINAL SMEAR	
	Normal
I SEVEN ANALYSIS	
	Normal
VIII ROENTGENOGRAPHIC FINDINGS	
A SKULL	
1 Cranial vault	Normal
2 Sella turcica	Normal
3 Sinuses	Normal
4 Mandible	Normal
5 Teeth	Normal, apical abscesses are common
B EPIPHYSEAL STATUS (bone age)	
	No retardation reported in children but the number of cases is too small for any definite conclusion ¹⁰⁴
C LONG BONES	
	Normal
D VERTEBRAE	
	Normal
E BONE TEXTURE	
	Normal possibly osteoporosis if disease is of a long duration
F MISCELLANEOUS	
1 Chest	Normal, active or healed tuberculosis heart size below the normal except when complicated with cardiac disease (see Fig 276) ¹¹⁰
2 Flat plate of abdomen	Positive signs of adrenal calcification may be found (31 5% of cases) ⁸⁸ or tumor

- (5) Hemorrhagic areas
- (6) Tuberculosis is never completely healed
- d Amyloidosis — particularly involves capillaries of cortex
- Tumors of cortex—see 42 I A B
- f Hemochromatosis — excessive deposition of
 - (1) Hemosiderin
 - (2) Hemofuscin
- g Blood vessel abnormalities
- 2 Pituitary—see 2 I A B 16
- 3 Lymphoid hyperplasia and infiltration of many organs
- 4 Heart—lysis of muscle fibers

XI PATHOLOGIC PHYSIOLOGY

A INTRODUCTION—Almost complete destruction or functional loss of both adrenal cortices is necessary to produce clinical signs or symptoms of adrenal insufficiency

B CARBOHYDRATE METABOLISM

- 1 Deficiency of sugar (S) hormones may be postulated
 - a Carbohydrate utilization is not impaired but possibly increased thus favoring hypoglycemia
 - b The immediate expenditure of amino acids for energy leads to
 - (1) Depletion of glycogen stores in
 - (a) Muscles
 - (b) Liver
 - (2) Hypoglycemia
 - c Failure to convert amino acids derived from protein and fat into liver glycogen⁴⁹
 - d Gastro intestinal effects
 - (1) Absorption of sugar is probably decreased
 - (2) Glucose tolerance curves
 - (a) Oral—flat type
 - (b) Intravenous — normal but severe hypoglycemic reactions may occur several hours later
 - e Insulin sensitivity ■ increased

C PROTEIN METABOLISM

- 1 Deficiency in nitrogen retaining and tissue synthesizing hormones may ensue
- 2 Essential amino acids may be used immediately for energy purposes (see above) thus denying these building

blocks for new tissue synthesis (or replacement)

- 3 A negative nitrogen balance is the eventual outcome

D SODIUM AND POTASSIUM METABOLISM

- 1 Deficiency in electrolytic hormones of adrenal cortex
- 2 Failure to conserve sodium and chloride, by loss through the renal tubules and sweat glands results in
 - a Withdrawal of fluid from intracellular spaces
 - b Decreased plasma volume due to redistribution of water
- 3 A decrease in urinary excretion of water and sweating occurs apparently in an attempt to save these electrolytes (see Table 53)
 - a When this measure fails a low blood sodium and chloride may be found
 - b This is the primary effect after adrenalectomy in animals⁵⁰
 - c Posterior pituitary antidiuretic substance may be increased⁵¹
- 4 Sodium and chloride are poorly absorbed by intestines further complicating the whole process
- 5 Retention of potassium due to a low urinary output leads to an increased concentration in the
 - a Blood
 - b Erythrocytes
 - c Skeletal muscle

E RESPIRATORY METABOLISM

- 1 Lowered metabolic rate including decreased tissue activity is not mediated through pituitary or adrenals
- 2 Respiratory quotient is elevated in patient with carbohydrate metabolic defects⁵²
- 3 Deficiency in various hormones especially epinephrine is basic factor

F CARDIOVASCULAR SYSTEM

- 1 Low blood pressure is not due entirely to loss of epinephrine but probably to deficient steroids as well
- 2 Sodium and weight loss favor hypotension

G DERMATOLOGIC METABOLISM

- 1 Mechanism of skin changes is not known
- 2 Findings are caused perhaps by an excess of an intermediary compound

- (10) Never healed³⁶
- (11) Total destruction³⁶
 - (a) Both \pm 80 per cent
 - (b) One and other incompletely \pm 20 per cent
- d Tumors
 - (1) Benign
 - (a) Encapsulated usually
 - (b) Cause pressure in
 - {1} Medulla
 - {2} Cortex
 - (2) Malignant
 - (a) Destructive
 - (b) Invasive
 - (c) Bilateral often, if metastatic or primary
- e Blood vessel disorders
 - (1) Emboli
 - (a) Flea bitten appearance, if multiple infected areas
 - (b) Gross infarction
 - (2) Thrombosis of adrenal veins
 - (a) Gross hemorrhagic diathesis
 - (b) Glands are
 - {1} Enlarged
 - {2} Dark red color
- f Amyloidosis
 - (1) Size
 - (a) Normal
 - (b) Increased slightly
 - (2) Color
 - (a) Gray
 - (b) Yellow
 - (3) Capsule—smooth
 - (4) Consistency—firm
 - (5) Zones well preserved
- g Hemochromatosis—cortex of adrenal contains excessive iron pigment
- h Various causes producing hemorrhage and altered conditions (gross appearance variable)
 - (1) Monilia
 - (2) Leukemia
 - (3) Syphilis
 - (4) Acute febrile disease
 - (5) Chemical poisoning
 - (6) Injury or wounds
 - (7) Meningococcus
 - (8) Typhus
- 2 Pituitary
 - a Atrophy may occur with tuberculosis of adrenals³³
 - b Capillary dilatation
- 3 Thyroid often shows lymphocytic infiltration³⁶
- 4 Ovaries and testes rarely affected³⁶
- 5 Lymphoid tissue
 - a Generalized hyperplasia
 - b Thymus reported enlarged in a few cases but evidence is not conclusive^{36 75}
 - c Spleen may be larger than normal in some cases³⁶
- 6 Gastro intestinal tract
 - a Ulcerations (small punched out areas) of
 - (1) Stomach
 - (2) Duodenum
 - (3) Jejunum
 - b True peptic ulcer in 22 per cent of autopsied cases³⁸
 - c Tuberculosis
- 7 Heart
 - a Color—brownish
 - b Size
 - (1) Normal
 - (2) Small usually
- 8 Lungs
 - a Normal
 - b Tuberculosis
 - (1) Healed
 - (2) Active
- 9 Other organs—tuberculosis may be found
 - a In most any organ
 - b Everywhere from miliary spread
- B MICROSCOPIC
 - 1 Adrenals^{1 9 25 36 41 55 9}
 - a Atrophy—'primary contracted adrenal'
 - (1) Loss or destruction of cortical cells
 - (2) Round cell infiltration of cortex
 - (3) Medulla may be spared
 - (4) Sclerosis
 - b Hypoplasia
 - (1) Cortex—decreased
 - (2) Medulla—normal
 - c Tuberculosis
 - (1) Medulla practically always involved
 - (2) Tubercles and tubercle bacilli are abundant
 - (3) Caseation with abscess
 - (4) Hyperplasia or small cortical adenomas

- c. Giddiness
- d. Vertigo
- e. Tinnitus
- f. Syncope
- g. Apathy
- h. Mental
 - (1) Depression
 - (2) Sluggishness
 - (3) Hallucinations
 - (4) Delusions
- i. Headache (rare)
- j. Irritability
- k. Convulsions and other symptoms due to hypoglycemia (see 85 \II)
- l. Muscular and joint pains and stiffness, may have associated rheumatoid arthritis
- m. Cold extremities
- 3 Cardiorespiratory
 - a. Few symptoms only
 - b. Breathlessness occasionally
 - Palpitation
- 4 Gastro-intestinal
 - a. Anorexia aversion to all foods
 - b. Nausea
 - c. Hicough
 - d. Vomiting
 - e. Diarrhea
 - (1) Constant
 - (2) Intermittent
 - (3) Common during crisis
 - f. Constipation
 - g. Abdominal discomfort or pain
 - (1) Mild
 - (2) Severe
 - h. Hemorrhage may occur
- 5 Genito-urinary
 - a. Males
 - (1) Loss of libido
 - (2) Impotence
 - b. Females
 - (1) Menstrual cycle remains normal in most cases - ⁶⁰ ₇₃
 - (2) Pregnancy may occur⁵¹ ₅₇
 - (3) Lactation is impossible
- b. Nausea vomiting and diarrhea may be present
- 2 Weakness and easy fatigability which are not complained of with a smile (patient's behavior consistent)
- 3 History of
 - a. Unconsciousness
 - b. Faintness
 - c. Convulsions with hypoglycemia
- 4 Bronze pigmentation on exposed areas of friction or black freckles on mucous membranes without any other symptoms do not always mean adrenal insufficiency
- 5 Normal or low blood pressure, if not found and other evidence is impressive inquire as to previous hypertension
- 6 Laboratory evidence
 - a. Decrease during crisis of
 - (1) Sugar (fasting)
 - (2) Sodium (serum)
 - (3) Chlorides (serum)
 - (4) Plasma volume
 - b. Increase (normal with hemoconcentration) during crisis
 - (1) Sodium (urinary)
 - (2) Chlorides (urinary)
 - (3) Hematocrit
 - (4) Nonprotein nitrogen (blood)
 - (5) Urea (blood)
 - (6) Protein (serum)
 - (7) Potassium (serum)
 - Water test—positive
- 7 Roentgenographic evidence of adrenal calcification in some cases (16%)
- 8 Provocative tests
 - a. Sodium deprivation (see 39 \III A 5 d)
 - (1) This is not recommended except in unusual cases
 - (2) The water test if positive in Part I and II is just as reliable supportive evidence and not fraught with danger
 - b. Adrenocorticotrophic hormone test (Thorn)¹ ₄ (see 39 \III A 5 c)
 - (1) Eosinophils show little or no drop in count
 - (2) Uric acid excretion is increased less than 30 per cent of normal
 - c. Epinephrine test—eosinophils show little or no change in count (see 39 \III A 5 b)⁵⁰

XIII DIAGNOSIS

A GENERAL SUMMARY

- 1 Unexplained gastro intestinal disturbances
 - a. Abdominal pain associated with
 - (1) Anorexia
 - (2) Weight loss

which is normally synthesized into epinephrine¹³

- 3 Pigmentation occurs in areas of
 - a Pressure
 - b Exposure to light
 - c Injury
- 4 Electrolytic composition of sweat (thermal) parallels the composition of urine, there is an increase of
 - a Sodium
 - b Chloride

TABLE 53 SWEAT TESTS¹⁸

	CHLORIDE CONCENTRATIONS IN MEQ/L.
Normal range	17.5 to 58.0
Adrenal cortical carcinoma with Cushing's syndrome	17 and 27
Adrenal cortical carcinoma with adrenogenital syn- drome	57 and 91
Cushing's syndrome with out carcinoma (2 cases)	59 to 135
Panhypopituitarism (3 cases)	68.0 to 75.0
Addison's disease (7 cases)	
Untreated	105.0 to 122.0
Treated	25.0 to 63.0

H ADAPTABILITY TO SHOCKING STIMULI

- 1 Sudden death in Addison's disease is often unexplained
- 2 Adrenalectomized animals are very sensitive to shocking stimuli
- 3 Loss of adrenocortical function should prevent the establishment of a counter shock phase in the alarm reaction (Selye) (see 99 II A 5)
- 4 Thymus and lymphoid involution and release of immune globulins may not occur
- 5 Hypoglycemia becomes severer because of failure to release adrenocortical carbohydrate hormones

I URINARY HORMONE ASSAYS

- 1 FSH—not increased
- 2 17 ketosteroids
 - a Absent in females
 - b Decreased in males
- 3 11 oxysteroids
 - a Absent
 - b Decreased

J SUMMARY

- 1 Apparently none of these altered func-

tions is the complete cause of adrenal insufficiency in animals or man

- 2 It is unlikely that these changes are entirely independent, but rather overlap in significant degrees
- 3 While desoxycorticosterone is thought to effect only sodium and potassium, the clinical improvement with this synthetic compound would indicate some action on sugar and protein metabolism as 123
- a There is also evidence that it prevents depletion of fat stores in the adrenalectomized animal
- b An increase in appetite may account for
 - (1) Greater protein intake
 - (2) Weight gain

XII SYMPTOMATOLOGY

A ACUTE (including adrenal crisis)

- 1 Onset may be sudden from
 - a An acute process as
 - (1) Infection
 - (2) Necrosis
 - b Exacerbation of an unsuspected or known chronic adrenal insufficiency case due to
 - (1) Above factors
 - (2) Salt restriction
 - (3) Hemorrhage
 - (4) Trauma
 - (5) Surgery
- 2 Fever (if acute infection)
- 3 Prostration
- 4 Abdominal pain, may be severe
- 5 Vomiting
- 6 Diarrhea
- 7 Hiccough
- 8 Tachycardia
- 9 Blood pressure, low
- 10 Anuria
- 11 Hypothermia
- 12 Sudden collapse (shock)
- 13 Coma

II CHRONIC

- 1 Gradual onset of asthenia
- 2 Neuromuscular and sensory
 - a Weakness
 - (1) With effort
 - (2) At rest
 - (3) On speaking
 - b Dimming of vision

- 4 Mucous membranes—normal
 - 5 Black freckles—absent
 - 6 Water test—may be positive
 - 7 ACTH test—normal
 - 8 17 ketosteroids—may be low
 - 9 Slight change with therapeutic use of
 - a Salt
 - b Glucose
 - c Desoxycorticosterone
 - 10 Improvement with adequate nutrition (voluntary or forced) (see 5 XIV A 106 III E)
- D CONVALESCENT STATES FROM INJURY IN INFECTIONS AND OPERATIONS** (see Adaptation syndrome 99)
- E HYPOPHYSITIS**
- 1 All or many signs and symptoms of primary adrenal insufficiency
 - 2 Notably absent or rare
 - a Diarrhea
 - b Weight loss which is
 - (1) Great
 - (2) Rapid
 - c Pigmentation
 - d Sexual hair
 - e Sexual function
 - 3 Sella turcica may be enlarged
- F POSTURAL HYPOTENSION (idiopathic)⁴**
- 1 Pulse rate does not rise with a fall in blood pressure when standing
 - 2 Effect is not through epinephrine for medulla is intact⁵⁰
- G HYPERINSULINISM**
- 1 Hypoglycemic symptoms occur at a blood sugar level of 50 mg % instead of 60 mg %¹¹¹
 - 2 No physical signs of adrenal insufficiency
- H DISEASES IN WHICH POSITIVE WATER TEST MAY BE PRESENT WITHOUT OTHER EVIDENCE OF ADRENAL INSUFFICIENCY**—see 39 VIII A 5 a (6) (7) ¹
- I SALT LOSING NEPHRITIS^{1, 2}**
- 1 Nonprotein nitrogen—elevated
 - 2 Carbon dioxide combining power—low
 - 3 Renal function—poor
 - 4 Failure to respond to desoxycorticosterone but possibly to cortisone
 - 5 Sodium chloride therapy—effective
- J DISORDERS ASSOCIATED WITH SODIUM LOSS LEADING TO SHOCK-LIKE CONDITIONS WITH NONPROTEIN NITROGEN RETENTION**
- 1 Diarrhea
 - a Prolonged
 - b Excessive
 - 2 Upper intestinal obstruction (fecal vomiting is unlikely in adrenal insufficiency)
 - 3 Ileostomy
 - 4 Diabetic acidosis
- XV COMPLICATIONS SEQUELAE OR ASSOCIATED DISEASES**
- A TUBERCULOSIS** (70 to 80% with adrenal tuberculosis)⁹
- 1 Pulmonary
 - 2 Glandular
 - 3 Renal
 - 4 Osseous
 - 5 Intestinal
 - 6 Visceral
- B CARCINOMA**
- 1 Adrenals primarily involved
 - 2 Metastatic
- C ADRENAL CRISIS PRECIPITATED BY**
- 1 Acute infection
 - a Tonsillitis
 - b Bronchopneumonia
 - c Pneumonia
 - d Dental sepsis with or without extraction (see Fig 278)
 - 2 Trauma
 - 3 Anesthesia
 - 4 Operation
- D OVERTREATMENT WITH**
- 1 Salt
 - a Edema may develop
 - b Blood pressure does not increase
 - 2 Desoxycorticosterone^{30 60 122 1 2}
 - a Edema
 - b Hypertension
 - c Cardiac enlargement
 - d Pericarditis
 - e Focal myocardial necrosis
 - f Arthralgias
 - g Nephritis
- E ASSOCIATED DISEASES**
- 1 Acromegaly
 - 2 Cushing's syndrome
 - 3 Myxedema
 - 4 Hyperthyroidism^{10 16 33 44}
 - 5 Hypoparathyroidism and moniliasis³
 - 6 Adrenogenital syndrome^{103 105}
 - 7 Diabetes mellitus (see Protocol 40 XXX)^{2, 3, 6, 7, 11, 14, 15, 17, 1 24, 63, 81, 83, 84, 86, 91, 121}

XIV DIFFERENTIAL DIAGNOSIS

A CONDITIONS WITH PIGMENTATION OF SKIN AND/OR MUCOUS MEMBRANES

- 1 Hemochromatosis
 - a It may be associated with adrenal insufficiency⁴⁵
 - b Mucous membranes are not pigmented
 - c Black freckles—absent
 - d Skin—bronze
 - e Enlargement of
 - (1) Liver
 - (2) Spleen
 - f Ascites—late in disease
 - g Glycosuria—often
 - h Hyperglycemia
 - i Positive test for iron in
 - (1) Skin biopsy
 - (2) Urinary cellular elements
- 2 Hyperthyroidism (see 26 XIII)
 - a Appetite—good
 - b Mucous membranes are not affected
 - c Black freckles—absent
 - d Skin pigmentation is increased, partly from weight loss; vitiligo is more common
 - e Thyroid—enlarged
 - f Tremor—fine
 - g Basal metabolic rate—increased
- 3 Myxedema (see 25 XIII)
 - a Skin
 - (1) Dry
 - (2) Thick
 - (3) Black freckles—absent
 - (4) Pigmentation
 - (a) Patchy
 - (b) Café au lait
 - b Cholesterol (plasma)—high
 - e Basal metabolic rate—usually much lower
- 4 Pellagra
 - a Pigmentation on exposed surfaces mostly hands and wrists
 - b Concomitant dermatitis—common
 - c Tongue—beefy red
 - d Delirium
 - e Diarrhea persists

NOTE The following can be easily eliminated by history and no signs, symptoms or laboratory findings of Addison's disease

- 5 Argyria
 - a History of using nose drops or other preparations containing silver

- b Mucous membranes are not involved
 - c Black freckles—absent
 - d Skin color is
 - (1) Bluish
 - (2) Silver gray
 - e Nails affected
- 6 Vitiligo
 - a Normal health
 - b Mucous membranes are not affected
 - 7 Chloasma (liver spots)—small, brown pigmented areas
 - 8 Internal medications
 - a Phenolphthalein
 - b Arsenic
 - c Bismuth—typical line on gums in some cases
 - 9 Pigmentation from external causes
 - a Sunburn
 - b Heat
 - c Irradiation (also atomic bomb)
 - d Local application of
 - (1) Lead
 - (2) Mercury
 - (3) Any skin irritant
 - 10 Racial groups
 - a The following have skin pigmentation similar to Addison's disease
 - (1) Ethiopians
 - (2) Orientals
 - (3) Latins
 - (4) Levantines
 - (5) American Indians
 - b Black freckles—absent
 - 11 Acanthosis nigricans
 - a Intra abdominal mass
 - b Evidence of malignant metastases
 - c Cutaneous biopsy is diagnostic
- B CHRONIC NERVOUS EXHAUSTION CONSTITUTIONAL INADEQUACY AND PSYCHASTHENIA
- 1 Long history consistent with above
 - 2 Weight loss is not significant
 - 3 Pigmentation if present is not characteristic
 - 4 Good one day bad the next
 - 5 Water test—normal in majority
 - 6 ACTH test—normal
 - 7 17 Ketosteroids—normal
- C ANOREXIA NERVOSA
- 1 Females affected more often than in Addison's disease
 - 2 Amenorrhea—more frequent
 - 3 Weight—loss usually without diarrhea

- d Cortisone may be given orally—25 mg/24 hrs
- e Pellets of DOCA implanted (see below)

II ACUTE ADRENAL INSUFFICIENCY

- 1 Occurring because of stress in a person maintained on DOCA therapy¹¹
- 2 Aqueous adrenocortical extract and/or cortisone (as above)—dosage dependent on
 - a Severity
 - b Speed of improvement
- 3 Saline solution intravenous—2 000 to 3 000 cc of 5 or 10 per cent glucose with saline (not over 10 Gm of salt/24 hrs)
- 4 Human plasma intravenous—250 cc¹¹⁵
- 5 Human albumen intravenous—500 to 1 000 cc of 5 per cent solution¹¹⁵
- 6 Potassium phosphate solution¹¹
 - a Mixture

(1) K_2HPO_4	20 Gm
(2) KH_2PO_4	04 Gm
(3) Glucose solution	10 per cent
 - b Addenda
 - (1) Human plasma
 - (2) Human albumen
- 7 Desoxycorticosterone acetate (DOCA) may be administered parenterally if reason to believe pellets are exhausted or inadequate
- 8 Penicillin—as above

C CHRONIC ADRENAL INSUFFICIENCY

- 1 Sodium chloride or sodium citrate
 - a Indications
 - (1) Relatively mild cases
 - (2) If no danger of crisis
 - (3) Better protection is afforded if DOCA is given even in mild cases
 - b Dosage
 - (1) Oral (capsules or enteric coated tablets)—0.5 to 1 Gm
 - (2) Wilder's solution*—50 to 100 cc a day depending on amount necessary to overcome acidosis
 - c Results
 - (1) Mild cases may be maintained with salt alone^{10 98}

* Citric acid	140 Gm
Sodium citrate	98 Gm
Water	1 000 cc

- (2) Salt alone will not cause hypertension
- (3) If optimal effects are not attained DOCA should be used (see below)

2 Desoxycorticosterone acetate (DOCA)

- a Indications
 - (1) Patients who cannot be maintained with sodium therapy alone
 - (2) Preferred in all cases (see Protocol 40 XXX)
- b Dosage
 - (1) Sublingual (not recommended)
 - (a) Tablets 1 mg every 2 hrs a day
 - (b) Propylene glycol alcohol (6 drops = 1 mg) As above¹³⁰
 - (2) Intramuscular (2 or 5 mg in oil) 2 to 5 mg a day or every other day
 - (3) Pellets (75 or 125 mg each) 1 to 6 (see below)
- c Method for determining dosage
 - (1) Parenteral route may be used to determine daily requirement although this is not necessary
 - (a) DOCA = injected daily in doses of 2.5 mg in oil
 - (b) Salt is used also about 1 Gm t.i.d.
 - (c) If there is no gain in weight in 3 days increase DOCA to 4 mg daily
 - (d) If the weight gain exceeds 0.5 kg a day or there is edema reduce the dose
 - (e) Injections may be used until patient is stabilized and then pellets are implanted
 - (f) One pellet should be used for each 0.3 mg a day
 - (2) Two (75 mg) pellets may be implanted safely if daily requirement is not known
 - (3) Average number required is 2 to 3 pellets
 - (4) If nonabsorption occurs or with exhaustion of pellets there is a

- 8 Paget's disease
- 9 Rheumatoid arthritis^{4*}
- 10 Acute infections
- 11 Ulcerative colitis
- 12 Nephritis^{7*}
- 13 Amyloidosis⁶

XVI TREATMENT

A ACUTE ADRENAL INSUFFICIENCY AND CRISIS

- 1 Bed rest and warmth
- 2 Adrenocortical medication
 - Indication—immediate substitution therapy
 - b Dosage
 - (1) Adrenocortical extract (aqueous), intravenous or intramuscular—25 to 100 cc or more, if patient is comatose
 - (2) Cortisone, parenteral—200 mg (may become available for intravenous use)

c Result—improvement with partial maintenance of blood sugar levels

3 Saline solution

- a Indications
 - (1) Restoration immediately of abnormal electrolytic balance due to salt loss
 - (2) Utilizable energy provided for saving body stores

b Dosage intravenous—2,000 to 3,000 cc of 0.9 to 1.5 per cent solution with 10 per cent glucose/24 hrs

c Results—striking improvement

4 Epinephrine hydrochloride

- a Aqueous solution
 - (1) Indication—to increase or maintain blood pressure
 - (2) Dosage—subcutaneous
 - (a) On admission—0.3 to 0.5 cc (1:1,000) if blood pressure is very low
 - (b) Later—repeat every 1 to 2 hrs as needed

(3) Results—value questionable

b Oil solution

- (1) Indication—as for aqueous extracts
- (2) Dosage subcutaneous—0.5 cc (1:500) once a day may be used in a few days in place of aqueous extracts

(3) Results—difficult to evaluate

5 Nor epinephrine (arterenol)

- Indication—as for epinephrine
- Dosage, intravenous drip—0.2 mcrograms/kg of body weight/min (2 mg/1 of saline)
- c Results—still experimental

6 Whole blood

- a Indications
 - (1) Anemia
 - (2) Weight loss of marked degree
- b Dosage, intravenous—500 cc.
- c Results—helpful

7 Human albumen^{11*}

- a Indications—as above
- b Dosage, intravenous—250 cc of 5 per cent solution
- Results—as above

8 Combined intravenous therapy^{11*}

- a Following may be given with 500 cc of 5 per cent glucose in normal saline solution
 - (1) Adrenal extract 50 to 100 units
 - (2) Penicillin 500,000 units
 - (3) Human albumen 25 Gm
- b From 250 to 500 cc of the above mixture may be given slowly

9 Protein hydrolysates are not^{11*}

- a Well tolerated
- b Recommended

10 Desoxy corticosterone acetate (DOCA)¹⁰

- a Indications
 - (1) Salt loss conserved
 - (2) Long term therapy initiated
- b Dosage—intramuscular
 - (1) First 24 hrs—5 to 20 mg
 - (2) Later—5 mg daily
- c Results—eliminates intravenous therapy in a few days

11 Penicillin¹⁰

- a Indications
 - (1) Fever
 - (2) Combat incipient infection
- b Dosage intramuscular—500,000 units daily
- c Results—favorable

12 When improvement is sufficient

- a Intravenous saline may be stopped
- b Salt in capsules may be substituted orally, if tolerated by patient
- c Cortical extract may be omitted or reduced to 5 cc a day

6 Diet

- a Low potassium diet is theoretically desirable but not actually necessary
- b Long periods of fasting should be avoided to prevent hypoglycemia therefore frequent feedings are advisable
- c Adequate caloric intake should be urged
- d Moderate carbohydrate and high protein diet should lessen the tendency to overproduction of insulin in view of
 - (1) Insulin sensitivity
 - (2) Rapid protein and fat conversion into sugar

7 Patient should have periodic examinations particularly during first few months of treatment

- a The following should be checked
 - (1) Weight
 - (2) Edema
 - (3) Blood pressure
 - (4) Pulse
 - (5) Heart size
 - (6) Fever
 - (7) Sedimentation rate
- b A rising blood pressure and edema which can be stopped before becoming marked are signs of DOCA overdosage (see below)
- Extreme loss of potassium may cause profound muscular weakness and flaccid paralysis due to^{118 123}
 - (1) General anesthesia
 - (2) Intravenous glucose
 - (3) Diarrhea
- d Patient should consult physician about any unusual variation in his condition or daily feeling of well being

D OVERDOSAGE OF DOCA OR SALT

- 1 Headache hypertension cardiac enlargement edema
 - a Salt intake stopped
 - b DOCA
 - (1) Injections are omitted temporarily
 - (2) Pellets may have to be removed
 - c Ammonium chloride oral (enteric coated tablets)—15 gr 4 to 6 times a day
 - d Potassium citrate (instead of am-

monium chloride) oral—4 to 8 cc in a 20 per cent solution in fruit juice 2 to 3 times a day¹¹⁷

- Adrenal cortical extract if needed
- f Mercurial diuretics

(1) Indication—in a grave condition, but its usage ■ not recommended¹¹⁷

(2) Dosage intramuscular or intravenous— $\frac{1}{2}$ to 1 cc

- 2 Muscular weakness tendon contractions and/or arthralgia¹¹⁶
 - a DOCA—discontinue or reduce dosage
 - b Adrenal cortical extract or cortisone may be substituted
 - c Potassium salts as above
- 3 Gynecomastia may develop⁷⁷ (also with adrenocortical extract⁸)

E CAUSES AND PREVENTION OF ADRENAL CRISIS

- 1 Careful adherence to program of treatment
- 2 Avoidance of unusual feats of
 - a Physical performance
 - b Severe emotional experiences
- 3 Safeguard against infection following tooth extraction and surgical operations by
 - a Penicillin or sulfa drugs prophylactically
 - b Protective dose of adrenal cortical extract or cortisone
 - c Adequate salt intake
 - d Saline and glucose infusions preoperatively and postoperatively
 - e Sufficient food intake especially the preceding night
- 4 With the onset of an acute upper respiratory infection patient should be instructed to
 - a Call physician
 - b Eat well
 - c Force fluids (fruit juices)
 - d Go to bed
 - e Keep warm
 - f Continue outlined therapy
 - g Take oral penicillin
 - (1) Should be kept on hand
 - (2) 200 000 units every 2 hrs in manner usually prescribed
- 5 Avoidance of
 - a Desiccated thyroid

- (a) Weight loss
- (b) Fall in blood pressure
- d Renewal of pellets (see Protocol 40, \\\)
- (1) This should be done when patient notes a
 - (a) Change in feeling of well being
 - (b) Weight loss
 - (c) Anorexia
- (2) Two to four (75 mg) pellets are usually sufficient for this purpose, depending on previous course
- Results
 - (1) Deliverance of 'hormone' from pellets
 - (a) Dependent on surface exposed and bodily needs
 - (b) Duration of effectiveness varies from 9 to 15 months
 - (2) Blood pressure rises
 - (3) Weight increases
 - (4) General health improves
- f Complications¹¹⁰
 - (1) Muscular weakness
 - (2) Tendon contractures
 - (3) Arthralgia
 - (4) Calcification of ear cartilages
- 3 Testosterone preparations^{6 10 103}
 - a Indication—in conjunction with DOCA for additional benefits
 - b Dosage (see Table 119 p 1,521)
 - (1) Sublingual or buccal tablets (methyltestosterone—10 mg each)

10 to 30 mg
a day
 - (2) Tablets (methyltestosterone—10 mg each)

20 to 60 mg
a day
 - (3) Parenteral (testosterone propionate—25 mg)

25 mg	3 to 6 times
	weekly
 - (4) Pellets (testosterone—75 mg)

4 (average)

 - Results⁴³
 - (1) Strength increases
 - (2) Weight gain
 - (3) General well being improves
- 4 Adrenocortical extracts
 - a Indications (expense precludes its use in most cases)
 - (1) Acute febrile disease
 - (2) Active tuberculosis
 - (3) Preoperatively and postoperatively, including dental surgery or extraction
 - b Preparations
 - (1) Adrenal cortical extracts
 - (a) Available commercially
 - (b) Contents are an assortment of cortical steroids which affect mineral as well as carbohydrate metabolism
 - (c) One analysis revealed around 10 mg of identified steroids per 50 cc of extract¹⁰⁷
 - (2) Aqueous extracts (parenteral)¹¹³
 - (a) Source—beef adrenals
 - (b) Twelve to 16 cc are equivalent to 1 mg of DOCA for salt metabolism
 - (3) Extract prepared in oil for parenteral use only¹¹³
 - (a) Source—hog adrenals
 - (b) Three cc are equivalent to 1 mg of DOCA for salt metabolism
 - c Dosage
 - (1) Aqueous solution (subcutaneous or intravenous)—20 to 50 units or cc in divided doses per day 3 to 7 times a week
 - (2) Oil preparation (intramuscular absorbed more slowly)—4 to 6 cc per day 3 to 7 times a week
 - d Results—is other preparations, except
 - (1) More effective as regards carbohydrate metabolism on account of 11 and 17 oxysteroid compounds^{108 1-3}
 - (2) Quicker in action
- 5 Cortisone (see 107 VIII M)
 - a Indications
 - (1) Supplemental to desoxycorticosterone therapy
 - (2) Pellets unnecessary
 - b Source—synthetic (from bile acids)
 - c Preparation—oral tablets
 - d Dosage—15 to 25 mg daily

ADDISON'S DISEASE WITH AN APPARENT ARREST
OF 6 YEARS' DURATION

Protocol XXX

Chief complaints For a year nausea, vomiting, epigastric pain weakness and loss of weight

Physical examination Age 47, female Weight 114 lbs BP 90/10 Skin diffusely pigmented, but without involvement of mucous membranes

Laboratory data RBC 4,900,000 Hgb 100% VPM 54 mg % Adrenal water test night volume 300 cc and day urine 8 30 A.M.—9 30 A.M.—94 cc 10 30 A.M.—27 cc 11 30 A.M.—21 cc 12 30 P.M.—15 cc Urine chloride 247 mg % Blood chloride 528 mg % Urine urea nitrogen 153 mg % Blood urea nitrogen 41.2 mg % Factor A = 3

Treatment Admitted to hospital Intravenous saline and glucose NPN decreased to 35 mg % Daily injection of DOCA followed by pellet implantation of 750 mg of DOCA Salt tablets could not be tolerated but liberal supply was used on food

Progress**YEARS**

- 5 No further treatment except salt Patient was well and active Marked loss

of pigmentation Weight rose to 132 lbs and remained there BP never below 140/80 Pellets not palpable Adrenal water test night urine over 100 cc, day urine 8 30 A.M.—50 cc 9 30 A.M.—150 cc 10 30 A.M.—150 cc, 11 30 A.M.—150 cc, 12 30 P.M.—160 cc

- 6 Patient began to lose weight and BP fell Gradual onset of asthenia Water test—Part I night urine 900 cc, day urine 9 30 A.M.—20 cc 10 30 A.M.—40 cc, 11 30 A.M.—20 cc Positive results 17 Letosteroids 0.5 to 4.8/24 hrs Pellets of DOCA (300 mg) implanted with immediate improvement which has been maintained

Comment Several explanations of the prolonged benefit of pellets are possible The pellets may actually have lasted the entire period or a functional strain on remnants of adrenal cortical tissue was relieved which with rest were able to carry on until insufficiency again developed possibly from an acute infection that was not noticed by patient

HYPERTHYROIDISM DIABETES MELLITUS AND
ADDISON'S DISEASE

Protocol XXX

History of present illness Age 33 female Hyperthyroidism (BMR plus 67 and plus 24%) and diabetes (fasting blood sugar 280 mg %) She was prepared with iodine and then had a subtotal thyroidectomy Subsequent BMR done each year for 5 years ranged from minus 4 to plus 11%

Treatment Diabetes was controlled with 10 units of protamine zinc insulin the first year 15 units the second year and the final average dose was 25 units

Progress**YEARS**

- 10 Patient had the grippe and diabetic acidosis Insulin requirement was increased to 50 to 70 units a day and subsequently was dropped to 15 units

of protamine zinc insulin and 10 units of regular insulin

- 10½ She noted a poor appetite, 6 lbs loss in weight pains in her legs and pigmentation of her skin Fasting blood sugar levels varied from 56 to 330 mg % Positive adrenal water test She was put on salt and advised to return for pellet implantation but before this was possible patient began to vomit and failed to report this to her physician She became semicomatose which was not due to insulin and died despite emergency treatment

Comment Pellet implantation of desoxycorticosterone is always advisable as soon as possible when severe diabetes is present with Addison's disease

- b Opiates
- c Barbiturates
- d Paraldehyde
- e Bromides
- f Insulin
- g Atropine
- h Histamine

6 Strict care in use of insulin, if also diabetic

F PREGNANCY⁸⁹

- 1 Early months of pregnancy and period of parturition present greatest hazards
- 2 Fetal adrenals may provide some replacement for mother's deficiency of adrenal hormones
- 3 Nausea and vomiting produce greater need for revised therapy
- 4 Management
 - a General—see above
 - b Delivery
 - (1) Before—treat as for impending crisis
 - (2) After—continue with same program for several days

G DIABETES⁹⁰ 3 6 7 1 14 15 17 -4 24 63 74 83 84 90 91 98 121

- 1 Association of the two diseases is rare
- 2 Diabetes mellitus may follow or precede Addison's disease or both develop simultaneously (see Protocol 40, XXX)
- 3 Water test may establish the diagnosis for adrenal insufficiency
- 4 When Addison's disease is found in a patient with diabetes mellitus, there is a reduction in (see Protocol 40, XXX)
 - a Glycosuria
 - b Hyperglycemia
 - c Insulin requirement
- 5 The marked sensitivity of patients with adrenal insufficiency to insulin persists, producing hypoglycemic attacks very readily
- 6 The insulin requirement is
 - a Less when patient is treated with salt or salt and DOCA
 - b Slightly increased with adrenal cortical extract or cortisone

XVII PROGNOSIS

A GENERAL

- 1 Unpredictable outcome but generally better in recent years

2 Dependent on

- a Etiology, for outcome is worse with
 - (1) Carcinoma of adrenals
 - (2) Active tuberculosis elsewhere in body (see 40 IX) if infection is quiescent or stationary, then prognosis is the same as with simple adrenal cortical atrophy
- b Severity of the process
- c Associated diseases
- d Adequacy and continuity of treatment
- e Degree of carbohydrate disturbance
- f Onset of symptoms
 - (1) Prognosis is good if the only signs are
 - (a) Pigmentation—a sudden increase may herald greater cortical loss⁹⁵
 - (b) Hypotension
 - (2) Prognosis is poorer with
 - (a) Gastro intestinal symptoms
 - (b) Weight loss
 - (c) Asthenia
 - (d) Fever

3 Age is not a factor, for life expectancy under 35 years is the same as in older group

B LIFE SPAN WITH THERAPY

- 1 Before modern methods—average about 12 months
- 2 With modern methods (since 1939)
 - a Average about 35 months¹⁰
 - b Fifty per cent survive 7 years¹¹⁹

XVIII CAUSES OF DEATH

A GENERAL

- 1 Acute adrenal insufficiency leads to death in itself due to a multiplicity of hormonal deficiencies
 - Shock
 - b Cerebral anoxemia
 - Renal failure
 - d Hypoglycemia⁴
 - Cardiac arrest possibly from low serum potassium¹¹⁸
- 2 Death may occur in coma even if blood sugar and electrolytic levels remain normal¹⁸
- 3 Acute fulminating infections⁴
- 4 Tooth extraction
- 5 Upper respiratory infection

- with Addison's disease *JAMA* 111 412-414 (July) 1938
- 27 Escamilla R F Diagnostic significance of urinary hormonal assays: report of experience with measurements of 17 ketosteroids and follicle stimulating hormone in the urine, *Ann Int Med* 30 249 290 (Feb.) 1949
 - 28 Etienne, M G Nouveau cas de maladie de Basedow et Addisonisme syndrome poly glandulaire par dysthyroïdie et dysurrenale *Bull et mem Soc méd d hop de Paris* 40 927 910 (June) 1916
 - 29 Falta W The Ductless Glandular Diseases Philadelphia Blakiston 1923 p 354
 - 30 Ferrebee J W Ragan C Atchley G W and Loeb R F Desoxycorticosterone esters: certain effects in treatment of Addison's disease *JAMA* 113 1725 1731 (Nov.) 1939
 - 31 Forbes A P Griswold G C and Albright F Clinical experience with a bioassay method for the determination of urinary corticosteroids *J Clin Endocrinol* 10 230 247 (Feb.) 1950
 - 32 Fraser R W, Albright F and Smith P H Value of glucose tolerance test, insulin tolerance test and glucose-insulin tolerance test in diagnosis of endocrinologic disorders of glucose metabolism *J Clin Endocrinol* 1 297 306 (Apr.) 1941
 - 33 Gitman L and Jacobs M Combined hyperthyroidism and adrenal cortical insufficiency: effect of iodine therapy: a case report *Ann Int Med* 19 507 514 (Sept.) 1943
 - 34 Gowen W M Addison's disease with diabetes mellitus *New England J Med* 207 577 5 9 (Sept.) 1932
 - 35 Greene C H Further studies in Addison's disease *Proc Staff Meet Mayo Clin* 6 305 310 (May) 1931
 - 36 Guttman P H Addison's disease: statistical analysis of 566 cases and study of pathology *Arch Path* 30 742 785 (Nov.) 895 935 (Dec.) 1930
 - 37 Harrop G A Westminster A Soffer L J and Trescher J H Diagnosis and treatment of Addison's disease *JAMA* 100 1850 1855 (June) 1933
 - 38 Harrop G A Soffer L J Ellisworth R and Trescher J H Studies on suprarenal cortex plasma electrolytes and electrolyte excretion during suprarenal insufficiency in dog *J Exper Med* 58 17 38 (July) 1933
 - 39 Helve O Electrocardiographic studies in Addison's disease *Ann med intern Fenn* 36 36 52 1947
 - 40 — A study of the metabolism in Addison's disease I On carbohydrate and phosphorus metabolism *Acta med Scandinav* 127 543 564 (May) 1947
 - 41 — A study of the metabolism in Addison's disease II On the metabolism of lipids, nitrogen and minerals and on the vitamin C balance *Acta med Scandinav* 128 1 24 1947
 - 42 Hoffman J Female Endocrinology including Sections on the Male Philadelphia Saunders 1944 p 589
 - 43 Hoffman W C Lewis R A and Thorn G W Electro-encephalogram in Addison's disease *Bull Johns Hopkins Hosp* 70 335 361 (Apr.) 1942
 - 44 Houston J C and Price T M L Addison's disease: a clinical review of thirty four cases with reports of three cases showing associated thyrotoxicosis *Gays Ho p Rep* 97 254 267 1943
 - 45 Hursthal L M Unpublished data
 - 46 Jaudon J C Addison's disease in children, *J Pediat* 28 73 755 (June) 1946
 - 47 — Addison's disease in an infant *J Clin Endocrinol* 6 558 564 (Aug.) 1946
 - 48 — Hypofunction of adrenals in early life *J Pediat* 29 696 710 (Dec.) 1946
 - 49 Kendall E C Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing New York 10th Meeting June 15 16 1945 pp 81 94
 - 50 Kenyon J., and Knowlton A Conference on Metabolic Aspects of Convalescence including Bone and Wound Healing 10th Meeting June 15 16 New York Josiah Macy Jr Foundation 1945 p 221
 - 51 Kepler E J., and Keating F R Diseases of adrenal glands: tumors of adrenal cortex diseases of adrenal medulla and allied disturbances *Arch Int Med* 68 1010 1036 (Nov.) 1941
 - 52 Kepler E J, Peters G A and Mason H L Addison's disease associated with pubic and axillary alopecia and normal menses *J Clin Endocrinol* 3 497-499 (Sept.) 1943
 - 53 Kepler E J and Wilson D M Diseases of adrenal glands Addison's disease *Arch Int Med* 68 979 1009 (Nov.) 1941
 - 54 Knowlton A I Mudge G H and Jailer J W Pregnancy in Addison's disease: report of four patients *J Clin Endocrinol* 9 514 528 (June) 1949
 - 55 Leonard M F Chronic idiopathic hypoparathyroidism with superimposed Addison's disease in child *J Clin Endocrinol* 6 493 506 (July) 1946
 - 56 Levenson S M Tagnon H J Goodpastor W L Green R W Taylor F H L and Lund C C Addison's disease associated with amyloidosis following thermal burns *New England J Med* 237 152 156 (July) 1947
 - 57 Levy M S Power M H., and Kepler E J Specificity of water test as diagnostic procedure in Addison's disease *J Clin Endocrinol* 6 607 632 (Sept.) 1946
 - 58 Lloyd C W and Lobotsky J Serum anti-diuretic substances and urinary corticosteroid in the human *J Clin Endocrinol* 10 318 329 (Mar.) 1950
 - 59 Loeb H F Chemical changes in blood in Addison's disease *Science* 76 420-421 (Nov.) 1932
 - 60 Maranon G La fonction sexuelle dans l'insuffisance urénale chronique *Presse med* 44 2057 060 (Dec.) 1936
 - 61 Margitay Becht A and Gomori P Die Nierenfunktion bei der Addisonischen Krankheit *Ztsch f d ges exper Med* 104 27 30 (Aug.) 1938
 - 62 Mason H L in Recent Progress in Hormone Research New York Acad Press 1948 Vol 3 pp 103 123
 - 63 McCullagh E P Two cases of diabetes mellitus one with myxedema and one with Addison's disease *Cleveland Clin Quart* 9 123 134 (July) 1942
 - 64 — Testicular dysfunction *Bull New York Acad Med* 24 341 363 (June) 1948
 - 65 McCullagh E P, Lewis L A and Owen W F Adrenal failure of pituitary origin

ACUTE ADRENAL INSUFFICIENCY FROM PRESUMED METASTATIC CARCINOMA OF THE LUNGS

PROTOCOL XXXI

Family history Negative*Past medical* Duodenal ulcer 8 years before*Chief complaints* Rather sudden onset of anorexia, nausea and vomiting and weight loss of 30 lbs*Physical examination* Age 45, male BP 110/70 Weak Slight tanning of skin No black freckles, but some brownish pigment of mucosa of mouth and gums Small supra clavicular lymph gland*Laboratory data* RBC 4,200,000 Hgb 10.8 Gm WBC 7,200 Differential polymorpho nuclears 69%, lymphocytes 24%, cosino

phils 7% Sodium chloride 528 mg % Water test positive, A factor 5.6 Biopsy of lymph node—metastatic undifferentiated carcinoma

Röntgenographic findings Lobulated mass arising in left mediastinum and extending to apex Probable carcinoma*Treatment* Intravenous saline, lipoadrenal extract, desoxycorticosterone and penicillin Temperature rose to 103° Pneumonic area in right lung Sudden death*Comment* Fifteen per cent of carcinomas of the lung metastasize to the adrenal glands *

REFERENCES

- Addison T Anaemia—disease of the supra renal capsules London Med Gaz 43 517 518 1849
- Adler D K Atypical Addison's disease associated with diabetes mellitus New England J Med 237 805 808 (Nov) 1947
- Allan F N Association of diabetes mellitus and Addison's disease Proc Staff Meet Mayo Clin 5 349 (Dec) 1930
- Anderson A B Tumor of adrenal gland with fatal hypoglycemia Am J Med Sc 180 71 79 (July) 1930
- Anderson E Haymaker W and Henderson E Successful sublingual therapy in Addison's disease JAMA 115 2167 2168 (Dec) 1940
- Armstrong C D Effect of testosterone propionate in a patient with diabetes mellitus and Addison's disease J Clin Endocrinol 4 23 29 (Jan) 1944
- Arnett J H Addison's disease and diabetes mellitus occurring simultaneously report of case Arch Int Med 39 698 704 (May) 1927
- Báez Villaseñor J Rath C E and Finch C A The blood picture in Addison's disease Blood 3 769 773 (July) 1948
- Barker N W Pathologic anatomy in 28 cases of Addison's disease Arch Path 8 432-450 (Sept) 1929
- Bartels E C Personal communication
- Bayliss R I S and Fraser R Addison's disease Proc Roy Soc Med 42 259 (Apr) 1949
- Bickel G Diabète pancréatique sévère devenu aglycosurique à l'occasion du développement d'une maladie d'Addison Helvet med acta 12 281 283 (June) 1945
- Bloch H Chemische Untersuchungen über das spezifische pigmentbildende ferment der Haut die Dopa-oxydase Ztschr f physiol Chem 98 226 254 1917
- Bloomfield A L Coincidence of diabetes mellitus and Addison's disease effect of cortical extract on glycemia and glycosuria Bull Johns Hopkins Hosp 55 456 465 (Dec) 1939
- Bowen H D and Koepf G F Metabolic changes in co existing diabetes mellitus and Addison's disease Endocrinology (Supp Assoc Proc) 30 1026 (June) 1942
- Broch J Addison's disease Acta med Scan dinav 125 395-408 1946
- Brookfield R W and Corbett H V Diabetes mellitus in association with degeneration of suprarenal glands Brit M J 1 231 232 (Feb) 1934
- Cawadiaz A F Adrenocortical cancer with undulating fever in Addison's disease J Clin Endocrinol 6 507 514 (July) 1946
- Conn J W, and Louis L H Production of endogenous salt active corticoids as reflected in concentrations of sodium and chloride of thermal sweat J Clin Endocrinol 10 12 23 (Jan) 1950
- Conn J W and Mathews K P Addison's disease in Negro Am J M Sc. 212 404-408 (Oct) 1946
- Curtis G M and Fertman M H Blood iodine in studies blood iodine in nonthyroid disease Arch Surg 54 541 555 (May) 1947
- Daughaday W H Jaffe H and Williams R H Adrenal cortical hormone excretion in endocrine and nonendocrine disease as measured by chemical assay J Clin Endocrinol 8 244 256 (Mar) 1948
- de la Balze F A Reifenstein E C Jr and Albright F Differential blood counts in certain adrenal cortical disorders (Cushing's syndrome Addison's disease and panhypopituitarism) J Clin Endocrinol 6 312 319 (Apr) 1946
- Devitt J S and Murphy F D Diabetes mellitus complicated by Addison's disease case report with a review of the literature Am J Digest Dis & Nutrition 14 164 (May) 1947
- Duffin J D Cortical necrosis of adrenal glands associated with Addison's disease report of 8 cases Arch Path 35 649 666 (May) 1943
- Edwards R A Shumkin M H and Shaver J S Hypertrophy of the breast due to injections of adrenal cortex extract in a man

- 112 *Ibid* p 52
- 113 *Ibid* p 85
- 114 *Ibid* p 92
- 115 *Ibid* p 93
- 116 *Ibid* p 144
- 117 *Ibid* p 147
- 118 *Ibid* p 149
- 119 *Ibid* p 156
- 120 — Treatment of Addison's disease *J Clin Endocrinol* 1 76 86 (Jan) 1941
- 121 Thorn G W and Clinton M Jr Metabolic changes in patient with Addison's disease following onset of diabetes mellitus *J Clin Endocrinol* 3 335 344 (June) 1943
- 122 Thorn G W Dorrance S S and Day E Addison's disease evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients *Ann Int Med* 16 1053 1096 (June) 1942
- 123 Thorn G W and Firor W M Desoxycorticosterone acetate therapy in Addison's disease clinical considerations *JAMA* 114 2517 2525 (June) 1940
- 124 Thorn G W, Forsham P H Prunty F T and Hills A G Test for adrenal cortical insufficiency the response to pituitary adrenocorticotrophic hormone *JAMA* 137 1005 1009 (July) 1948
- 125 Thorn G W Garbutt H R Hitchcock F A and Hartman F A Effect of cortin on sodium potassium chloride inorganic phosphorus and total nitrogen balance in normal subjects and in patients with Addison's disease *Endocrinology* 21 202 212 (Mar) 1937
- 126 Thorn G W Howard R P and Emerson K Jr Treatment of Addison's disease with desoxy corticosterone acetate synthetic adrenal cortical hormone (preliminary report) *J Clin Investigation* 18 449 467 (July) 1939
- 127 Thorn G W Howard R P Emerson K Jr and Firor W M Treatment of Addison's disease with pellets of crystalline adrenal cortical hormone (synthetic desoxy corticosterone acetate) implanted subcutaneously *Bull Johns Hopkins Hosp* 64 339 365 (May) 1939
- 128 Thorn G W Koepf H F, and Clinton M Jr Renal failure simulating adrenocortical insufficiency *New England J Med* 231 16 85 (July) 1944
- 129 Thorn G W, Koepf G F Lewis R A and Olsen E F Carbohydrate metabolism in Addison's disease *J Clin Investigation* 19 813 832 (Nov) 1940
- 130 Turnoff D and Rowntree L G Successful sublingual therapy in Addison's disease *JAMA* 116 2016 (May) 1941
- 131 Venning H Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing 10th Meeting June 15 16 New York Josiah Macy Jr Foundation 1945 pp 150 191
- 132 Venning E H and Browne J S L Excretion of glycoenic corticoids and of 17 ketosteroids in various endocrine and other disorders *J Clin Endocrinol* 7 79 101 (Feb) 1947
- 133 Wang F C and Verzar F Comparison between glycoenic property of desoxycorticosterone 11-dehydro 17 hydroxycorticosterone (compound E) and adrenal cortical extract *Am J Physiol* 159 263 268 (Nov) 1949
- 134 Waterhouse C and Keutmann E H Kidney function in adrenal insufficiency *J Clin Investigation* 27 373 379 (May) 1948

- plasma protein studies (Tischus) report of 4 cases, *Cleveland Clin Quart* 10 88 104 (July) 1943
- 66 McCullagh E P and Ryan E J Use of desoxycorticosterone acetate in Addison's disease *JAMA* 114 2530 2537 (June) 1940
 - 67 McCullagh E P Schneider R W Bowman W and Smith M H Adrenal and testicular deficiency a comparison based on similarities in androgen deficiency androgen and 17 ketosteroid excretion and on differences in their effects upon pituitary activity *J Clin Endocrinol* 8 275 294 (Apr) 1948
 - 68 McGavack T Charlton G P and Motz S Effect of desoxycorticosterone acetate on glucose tolerance in normal individuals and in patients with Addison's disease *J Clin Endocrinol* 1 824 830 (Oct) 1941
 - 69 McQuarrie I Johnson R M and Ziegler M R Plasma electrolyte disturbance in patient with hypercortisoadrenal syndrome contrasted with that found in Addison's disease *Endocrinology* 21 762 772 (Nov) 1937
 - 70 Meissner W H Personal communication
 - 71 Millis G C and Coneybeare J J Addison's disease treated in Guy's Hospital between 1904 and 1923 *Guy's Hosp Rep* 74 369 375 (Oct) 1924
 - 72 Muscio Fournier J C Pollack E and Lusich Sir J J Loss of axillary and pubic hair in a patient with Addison's disease and regular menstruation *J Clin Endocrinol* 9 555 556 (June) 1949
 - 73 Muscio Fournier J C and Proto A Un cas de maladie d'Addison avec absence de poils axillaires et pubiens malgré la conservation de la menstruation *Bull et mem Soc med d'hop de Paris* 63 62 63 1947
 - 74 Nix N W Diabetes mellitus associated with Addison's disease *Canad M A J* 49 189 191 (Sept) 1943
 - 75 Pappenheimer A M Contribution to normal and pathological histology of thymus gland *J Med Res* 22 1 74 (Feb) 1910
 - 76 Prunty F T G The use of adrenocorticotrophin in testing for adrenal insufficiency *Proc Roy Soc Med* 42 267 270 (Apr) 1949
 - 77 Raleigh H W and Philipsborn H F Jr Case report Addison's disease with partial absence of adrenal cortex and gynecomastia *Arch Path* 37 213 215 (Mar) 1944
 - 78 Raverby L and Sawyer W H Addison's disease complicated by chronic glomerulonephritis *New England J Med* 239 110 112 (July) 1948
 - 79 Rawson A J Collins L H and Grant J L Histoplasmosis and torulosis as causes of adrenal insufficiency *Am J M Sc* 215 363 371 (Apr) 1948
 - 80 Recant L Hume D M Forsham P H and Thorn G W Studies on the effect of epinephrine on the pituitary adrenocortical system *J Clin Endocrinol* 10 187 229 (Feb) 1950
 - 81 Reifenstein E C *Endocrinology a synopsis of normal and pathologic physiology diagnostic procedures and therapy* M Clin North America 28 123 1276 1944
 - 82 Reifenstein E C Forbes A P, Albright F, Donaldson E and Carroll E Effect of methyltestosterone on urinary 17 ketosteroids of adrenal origin *J Clin Investigation* 24 416 434 (July) 1945
 - 83 Rhoad E G III and Wilson A Diabetes mellitus in Addison's disease *Lancet* 2 37 38 (July) 1941
 - 84 Rogoff J M Addison's disease following adrenal denervation in case of diabetes mellitus *JAMA* 106 279 281 (Jan) 1936
 - 85 Rowntree L G and Snell A M A Clinical Study of Addison's Disease Mayo Clin Monographs Philadelphia Saunders 1931
 - 86 Rowntree L G and Snell A M G Diseases of suprarenal glands *Endocrinology* 17 263 294 (May June) 1933
 - 87 Samuels L T, Evans G T and McKelvey J L Ovarian and placental function in Addison's disease *Endocrinology* 33 422 428 (May) 1943
 - 88 Schuttinheim A and Buhler F Die Beeinflussung der Spontansekretion innersekretorischer Störungen durch Hormone des Hypophysenvorder und hinterlappens der Schilddrüse und der Nebenniere *Ztschr f d' exper Med* 95 206 213 1935
 - 89 Sheldon D E Pregnancy complicated by Addison's disease *Am J Obst & Gynec* 49 269 272 (Feb) 1945
 - 90 Simpson S L Addison's disease and its treatment by cortical extract *Quart J Med* 1 99 133, 1932
 - 91 — Addison's disease and diabetes mellitus in three patients *J Clin Endocrinol* 9 403 435 (May) 1949
 - 92 Snell A M Treatment of Addison's disease *Proc Staff Meet Mayo Clin* 9 57 61 (Jan) 1934
 - 93 Soffer L J Diseases of the Adrenals Philadelphia Lea & Febiger 1946 p 56
 - 94 *Ibid* p 97
 - 95 *Ibid* p 98
 - 96 *Ibid* p 100
 - 97 *Ibid* p 109
 - 98 *Ibid* pp 110 113
 - 99 *Ibid* p 114
 - 100 *Ibid* p 115
 - 101 *Ibid* pp 116 121
 - 102 Talbot N H Albright F, Saltzman A H, Zygmuntowicz A and Wixom R The excretion of 11 oxycorticosteroid like substances by normal and abnormal subjects *J Clin Endocrinol* 7 331 350 (May) 1947
 - 103 Talbot N B Butler A M and MacLachlan B A Effect of testosterone and allied compounds on mineral nitrogen and carbohydrate metabolism of a girl with Addison's disease *J Clin Investigation* 33 583 593 (July) 1943
 - 104 Talbot N H and Sobel E H in *Advances in Pediatrics* New York Interscience 1947 Vol 2 pp 210 273
 - 105 Thelander H E Congenital adrenal cortical insufficiency associated with macrogenitosomia follow up and terminal report *J Pediat* 39 213 221 (Aug) 1946
 - 106 Thomas H M Jr Meningococcal meningitis and septicemia report of outbreak in Fourth Service Command during winter and spring of 1942 1943 *JAMA* 123 264 272 (Oct) 1943
 - 107 Thorn G W The Diagnosis and Treatment of Adrenal Insufficiency Springfield Ill Thomas 1949 p 15
 - 108 *Ibid* p 16
 - 109 *Ibid* p 29
 - 110 *Ibid* p 32
 - 111 *Ibid*, p 33



FIG 272 ADDISON'S DISEASE (See also Figs 271 and 273) Addison's disease with marked pigmentation of arms as compared with the normal (left)



FIG 273 ADDISON'S DISEASE (See also Figs 271 and 272) Pigmentation of mucous membranes of lips. Note that beard growth is normal



FIG 274 ADDISON'S DISEASE
Chief complaints Weakness pigmentation of skin for 3 years Weight loss of 17 lbs Amenorrhea 2 years
Physical examination Age 34 female As above BP 150/90 Darkly pigmented especially about elbows knees and perineum Black freckles Loss of axillary and pubic hair
Laboratory data Positive water test
Röntgenographic findings Skull negative Chest negative No calcification of adrenals
Comment No further investigation could be done Hypopituitarism cannot be excluded as cause of adrenal insufficiency in this case but pigmentation and black freckles are in favor of primary cortical atrophy



FIG 270 ADDISON'S DISEASE (Left) Picture of original case (Henry Patten) of Thomas Addison (Right) Organs of same patient (Top) Diseased suprarenal capsules in situ (Bottom) Sections of suprarenal capsules (Addison T On Disease of Supra Renal Capsules London Samuel Highley)

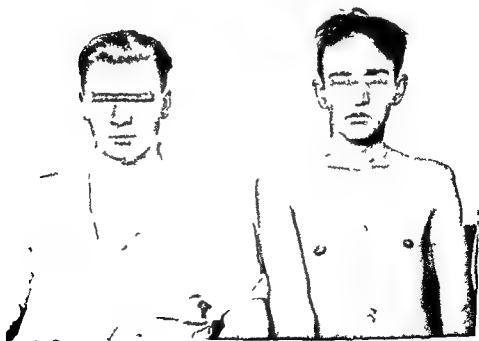


FIG 271 ADDISON'S DISEASE (See also Figs 272 and 273) A patient with Addison's disease showing generalized pigmentation compared with the normal (left)

FIG 277 ABSCESSSED TUBERCULOUS ADRENAL GLAND Adrenalectomy was performed in a patient with Addison's disease because of a tuberculous abscess. Recovery and maintenance on desoxy corticosterone



FIG 278 ADDISON'S DISEASE

History Age 40 female Loss of weight (40 lbs) and strength Nausea and vomiting 6 months

Progress After hospital treatment patient did well on salt (8 Gm/24 hrs) and adrenocortical extract (Wilson) 4 cc weekly Patient felt well for 5 years until a tooth was extracted at home After that she rapidly developed swelling and pain in the jaw and tissues of the face and neck In spite of intravenous fluids of saline and glucose cortical extract sulfathiazole and DOCA patient died in 36 hrs

Postmortem Healed tuberculosis of both adrenals No normal adrenal tissue was found

Comment Tooth extraction is a serious undertaking in Addison's disease Careful preparation is of utmost importance

(Left) Shortly after initial treatment (Right) Several years later Note decrease in pigmentation



FIG 275 RAPID PIGMENTATION OF ADRENAL INSUFFICIENCY FOLLOWING REMOVAL OF ADRENAL TUMOR

Chief complaint Gallbladder trouble for 9 years

History of present illness Repeated attacks of severe right upper quadrant pain with

nausea and vomiting Patient required hypodermics for relief No other complaints Roentgenograms showed gall stones Patient lost 30 lbs on a reduction diet

Physical examination Age 33 female BP 110/60 Normal findings

Roentgenographic findings One large gall stone and a mass 10 cm in diameter flecked with calcium

Treatment Cholecystectomy Right adrenal removed because of adrenal tumor which was reddish in color firm and speckled with areas of calcification Left adrenal was palpated and considered normal She had a severe postoperative shock but recovered with adrenal therapy

Pathologic report Cortical carcinoma with old hemorrhage and bone formation Gall stones

Progress Within a month the patient developed typical Addison's disease a bronze color numerous black freckles and pigmentation of the operative scar BP 90/40 Positive water test She was maintained on desoxycorticosterone Weight 3 years later was 130 lbs Patient working Menses normal Note marked pigmentation of hands and abdominal scar

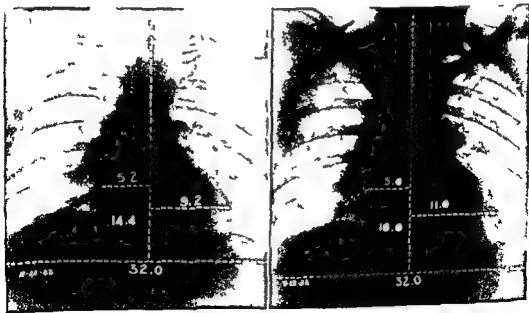


FIG 276 ADDISON'S DISEASE Heart size in 56 year old man with previous hypertension before and 7 months after treatment with desoxycorticosterone pellets (*Left*) Weight 164 lbs BP 90/60 at time of first roentgenograms Note hypertensive shape of heart (*Right*) Weight 151 lbs BP 160/110

- | | |
|-----------------|-------------------------------------|
| 5 Chlorides | Normal ^{4 13} |
| 6 Creatinine | Increased ⁴ |
| 7 Icterus index | Normal or increased ^{4 13} |

D MISCELLANEOUS

- 1 Blood culture
 - a Meningococcus in 50 per cent¹²
 - b Other organs have been reported but relationship is unknown
- 2 Spinal fluid
 - a Cells Normal or increased rarely
 - b Pressure Normal
 - c Culture Meningococcus infrequently

VIII ETIOLOGY**A TYPES**

- 1 Newborn
 - a Asphyxia
 - b Trauma
 - c Toxemia
 - d Syphilis
- 2 Childhood or adulthood
 - a Meningococcal septicemia without purulent meningitis - Martland is of the opinion that this organism is the sole cause of the acute syndrome¹³
 - b Other organisms have been reported
 - (1) Staphylococcus
 - (2) Streptococcus
 - (3) Pneumococcus
 - c Acute infections^{3 5 6 8-10 1 16 20}
 - (1) Diphtheria
 - (2) Scarlet fever
 - (3) Pneumonia
 - (4) Polomyelitis
 - (5) Pemphigus
 - (6) Hemophilus influenza
 - d Heparin therapy¹⁹

3 Meninges—rarely involved even in cases due to meningococemia

4 Brain

- a Vessels of leptomeninges are congested
- b Convulsions flattened
- c Encephalitis is not common

5 Thymus and lymph glands

- a Enlarged
- b Hyperplasia

6 Other organs—findings of a fulminating infection

X SYMPTOMATOLOGY^{1 3 7 13 14 17 21}**A Onset—Sudden following**

- 1 Mild upper respiratory infection
- 2 Gastro-intestinal complaints (mild)
- 3 Good health

B GENERAL

- 1 Fever rises rapidly
- 2 Chill or chilly sensations
- 3 Irritability
- 4 Headache
- 5 Muscular aches
- 6 Stiffness of neck occasionally
- 7 Nausea
- 8 Vomiting
- 9 Abdominal pain
- 10 Respirations increased

C Course

- 1 Fulminating
- 2 Rapid downhill
- 3 Death within 24 hrs rarely 80 to 88 hrs

XI DIAGNOSIS**A History**

- 1 Sudden onset of an acute illness
- 2 Few mild complaints followed by severe prostration in a short while

IX PATHOLOGY**A GROSS AND MICROSCOPIC^{7 9 11 13 17}**

- 1 Adrenals
 - a Hemorrhage
 - (1) Bilateral
 - (2) Diffuse and minute to massive with rupture of the capsule occasionally
 - b Medulla and zona reticularis are principal sites of damaged tissue
 - c Suprarenal vein thrombosis is uncommon
- 2 Skin—lesions are due to capillary and arteriolar
 - a Breakage
 - b Occlusion

SECTION 41

WATERHOUSE-FRIDERICHSEN SYNDROME

SYNONYMS

Suprarenal apoplexy
Spontaneous suprarenal hemorrhage
Purpura fulminans

I DEFINITION

An acute hemorrhagic disease of the adrenals that occurs most frequently in infants and young children and which may be rapidly fatal

II APPEARANCE

Acutely and critically ill patient who is dyspneic, cyanotic, stuporous or comatose, showing petechiae or purpuric rash, and often signs of shock

III AGE

Infants or young children, rarely adults¹⁶

IV SEX

Either

V MENTAL DEVIATIONS

Stuporous or comatose in most cases

VI PHYSICAL STATUS

A GENERAL

- 1 Respiration
- 2 Temperature
- 3 Petechiae

Grunting

Elevated, chills frequent

First at conjunctivae extremities trunk, increase quickly to large purpuric rash, later confluent, when due to hemorrhagic disease of newborn, fewer spots are present¹

- 4 Color
- 5 Pulse
- 6 Blood pressure
- 7 Neurologic

Cyanosis

Rapid and shallow

Falls, circulatory collapse

May be negative later convulsions, coma, death

VII LABORATORY DATA

A URINE

- 1 Sediment
- 2 Volume

Albumin and casts may be present

Reduced

B HEMATOLOGY

- 1 Red blood cells
- 2 Hemoglobin
- 3 White blood cells
- 4 Differential

May be decreased

May be decreased

Normal to 99,500¹⁷

Increased polymorphonuclear leukocytes relative lymphopenia

- 5 Platelets
- 6 Bleeding time
- 7 Coagulation time

May be reduced

Normal¹¹

Normal¹¹

C BLOOD CHEMICAL ANALYSES

- 1 Sugar
- 2 Nonprotein nitrogen
- 3 Sodium
- 4 Potassium

May be decreased

Increased⁴

Normal, may be increased⁴

Normal may be increased⁴

SECTION 42

THE ADRENOGENITAL SYNDROMES

I DEFINITION

A INTRODUCTION

- 1 The adrenogenital syndromes may be defined as a complex of signs and symptoms resulting from excess secretion of androgenic hormones by adrenal cortical tissue
- 2 The manifestations of the adrenogenital syndromes depend upon the
 - a Age of onset
 - b Initial sex of the individual (genetically speaking)¹⁹
 - c Type and amount of hormones elaborated
- 3 The signs and symptoms are those of
 - a Precocious sexual and somatic development of young males
 - b Masculinization and varying degrees of increased somatic develop-

ment in fetal, young or adult females

- 4 Except for the divergent abnormalities of the genital apparatus other changes are somewhat similar in all types
- 5 Feminization of the male due to adrenocortical hyperfunction is not usually classified under adrenogenital syndromes (although there is little doubt that it should be) (see 43 VIII XII)
- 6 Cushing's syndrome may also be due to hypercorticoadrenahism but the non androgenic cortical hormones predominate therefore it is a distinct and different clinical entity (see 11)
- 7 Achard Thiers syndrome (diabetes of bearded women) — a rare condition manifesting combined hyperadrenal corticalism of the Cushing's and adrenogenital syndromes (see 84 XIV B 5)^{1, 20}

II APPEARANCE

A JUVENILE

Variable obese muscular slightly over average height carp mouthed hirsute (see Figs 279 and 280)

B ADULT

Normal to obese feminine or masculine configuration, fat cheeks often hirsute temporal hair recession occasionally and acne (for pseudohermaphroditism of adrenal origin see 80 IV)

III AGE

Any

IV SEX

Either but females predominate

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal or below average¹⁷

B RESPONSIVENESS

Normal variations

C OTHER ABERRATIONS

Females may have male psyche

VI PHYSICAL STATUS

A NUTRITION

Normal

1 Weight

Normal

2 Fat

Masculine tendency

B STATURE

During growth period may be taller than average because of precocious development but epiphyseal closure occurs sooner so that final height is often below standard (see Fig 280 and Chart 94)^{17 24 26 29}

C EXTREMITIES

1 Upper

Normal or masculine configuration

a Hands

Proportionate to increased developmental changes

b Fingers

As above

II FINDINGS

- 1 Vasomotor collapse
- 2 Acute adrenal insufficiency
- 3 Meningococcal infection in some cases

XII TREATMENT

A COMMENT

- 1 Immediate and vigorous therapy must be instituted because of fulminating course of the disease
- 2 Combat
 - a Acute adrenal insufficiency
 - b Infection
 - c Vasomotor collapse

B MANAGEMENT

- 1 Infection
 - a Sulfonamides
 - b Penicillin
 - c Saline and glucose (intravenous)
 - d Whole blood transfusions
- 2 Adrenal insufficiency (see 40 XVI)
 - a Whole adrenal extract¹⁵
 - b Desoxycorticosterone
 - c Cortisone—large doses

d Saline and glucose (intravenous)

e Adrenalin, possibly

3 Miscellaneous

a Vitamin C, optional

b Oxygen, if necessary

C RESULTS OF THERAPY

- 1 Decrease in pigment is not due to a loss, but to improved hydration
- 2 Improvement with saline
- 3 Better effect on muscles with adrenocortical extracts than desoxycorticosterone however, the latter is very beneficial

XIII PROGNOSIS

A IN THE PAST—Fatal for all

B RECENT RESULTS—Recovered cases have been reported^{9 14 17 1}

XIV CAUSES OF DEATH

A ACUTE ADRENAL INSUFFICIENCY

B MENINGOCOCCEMIA

C UNKNOWN

REFERENCES

- 1 Aegerter E E Waterhouse Friderichsen syndrome review of literature and report of 2 cases. *JAMA* 106 1715 1719 (May) 1936
- 2 Bernhard W C and Jordan A C Bilateral adrenal hemorrhage associated with meningococcal septicemia. *J Lab & Clin Med* 29 357 365 (Apr) 1944
- 3 Ceballos A, Frank T V and Simpson W F Jr Waterhouse Friderichsen syndrome report of 8 cases at Children's Hospital Washington D C. *J Pediat* 27 281 287 (Sept) 1945
- 4 Dagati V C and Marangoni B A Friderichsen syndrome. *New England J Med* 232 17 (Jan) 1945
- 5 Firor W M Adrenal hemorrhage in children. *South M J* 30 306 309 (Mar) 1937
- 6 Ginandes G J and Howard J E Case of Waterhouse Friderichsen syndrome due to hemophilus influenza. *J Mt Sinai Hosp* 14 778 783 (Sept Oct) 1947
- 7 Goldzieher M A and Gordon M B Syndrome of adrenal hemorrhage in newborn. *Endocrinology* 16 165 181 (Mar Apr) 1932
- 8 Hurter L E Suprarenal haemorrhage complicating puerperium. *Proc Roy Soc Med* 39 581 583 (July) 1946
- 9 Kinsman J M D Alonzo C A and Russi A Fulminating meningococcal septicemia associated with adrenal lesions. *Arch Int Med* 78 139 169 (Aug) 1946
- 10 Kunststadter R H Waterhouse Friderichsen syndrome. *Arch Pediat* 56 489 492 (Aug) 1939
- 11 Leone G E Spontaneous hemorrhage into suprarenals (suprarenal apoplexy). *Ann Int Med* 14 2137 2142 (May) 1941
- 12 Lindsay J W Rice E C Selinger M A and Robins L Waterhouse Friderichsen syndrome acute bilateral suprarenal hemorrhage. *Am J Med Sci* 201 263 270 (Feb) 1941
- 13 Martland H E Fulminating meningococcal infection with bilateral massive adrenal hemorrhage (Waterhouse Friderichsen syndrome) with special reference to pathology, medicolegal aspects and incidence in adults. *Arch Path* 37 147 158 (Feb) 1944
- 14 Peabody S D Purpura fulminans (Waterhouse Friderichsen syndrome) report of case with recovery. *New England J Med* 229 934 936 (Dec) 1943
- 15 Smith M H D Waterhouse Friderichsen syndrome its treatment with adrenal cortex extract. *Am J Dis Child* 69 330-331 (May) 1945
- 16 Snelling C E and Erb I H Hemorrhage and subsequent calcification of suprarenal. *J Pediat* 6 22-41 (Jan) 1935
- 17 Soifer L J Diseases of the Adrenals, Philadelphia Lea & Febiger 1946 pp 127 130
- 18 Thomas H M Jr Meningococcal meningitis and septicemia report of outbreak in Fourth Service Command during winter and spring of 1942. *JAMA* 123 264 277 (Oct) 1943
- 19 Verdonk G J Adrenal hemorrhage following hepatic therapy. *Nederl tijdschr v geneesk* 91 2409 2412 (Aug) 1947
- 20 Wasserman C F Waterhouse Friderichsen syndrome. *New Orleans M J* 88 286 293 (Dec) 1946
- 21 Wright D O and Reppert, L B Fulminating meningococemia with vascular collapse (Waterhouse Friderichsen syndrome). *Arch Int Med* 77 143 150 (Feb) 1946

3 Hernia	None
4 Tumor	Present in some cases at kidney area
L GENITALIA	
1 Male ^{7 17 20 32 38 44 60}	
a Penis	Increased size in young males
b Testes	Normal for chronologic age may increase at usual time of puberty
c Prostate	May be enlarged for age
2 Female ^{7 0 4 31 46 49}	
a External	Clitoris may hypertrophy to size of male penis of same age vulva enlarged (see Fig 281)
b Internal	Retarded development in a few cases, vestigial female prostate may enlarge
M NEUROMUSCULAR	
1 Muscles	Bulk relatively increased but not always
2 Gait	Normal or strutting
3 Body movements	As if an older person
4 Tremor	None
5 Paresthesias	None
6 Reflexes	None
N SPEECH	Normal
VII LABORATORY DATA	
A URINE	
1 General	Normal
2 Special analyses	
a Sugar	Normal
b Albumin	Normal
c Creatine	Increased excretion probably commensurate with muscle mass
d Creatinine	Normal
e Chlorides	Normal ⁴
B HEMATOLOGY	
1 Red blood cells	Normal or increased ⁴
2 Hemoglobin	Normal
3 White blood cells	May be increased
4 Differential	Normal or polymorphonuclears increased
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal or increased ^{20 33 46 46 60}
2 Nonprotein nitrogen	Normal or increased ^{4 40 46 60}
3 Protein	Normal or decreased ⁴⁰
4 Uric acid	Normal
5 Cholesterol	Normal ^{40 60}
6 Sodium	Normal
7 Potassium	Normal
8 Calcium	Normal ^{4 8 46 46 60}
9 Phosphorus	Normal or increased for age decreased rarely ^{20 3 46 60}
10 Phosphatase	Normal ⁶
11 Chlorides	Normal ^{4 40 46}
D FUNCTION TESTS	
1 Tolerance	
a Glucose	Normal or rarely unpaired ^{7 24 46 63}

c	Span	Normal
2	Lower	Pubis to floor may be less than pubis to head ⁴⁰
a	Feet	As above
b	Toes	As above
D	SPINE	Normal
E	INTEGUMENT	
1	General	Normal
a	Texture	Lacks baby softness
b	Temperature	Normal
c	Eruptions	Acne with virilism
d	Pigmentation	Nothing unusual
e	Color	Normal
2	Hair (see Fig 279)	
a	Head	Plentiful, low browed, later temporal recession, rarely baldness in females
b	Facial	May be increased in normal places as well as on neck, eyebrows may be heavy
c	Axillary	Normal or more than for age
d	Pubic	Increased for age, male distribution may occur in females
e	Body	Normal or increased (marked in some)
F	HEAD	
1	Shape and size	Normal
2	Facial expression	Not unusual
3	Eyes	
a	General	Normal
b	Fundi	Normal
c	Visual	
(1)	Fields	Normal
(2)	Acuity	Normal variations
4	Ears and nose	Normal
5	Mouth and throat	Normal
a	General	Normal
b	Teeth	Normal or development accelerated ¹⁷
c	Larynx (voice)	Normal or lowered
G	NECK	
1	General	Normal or thick occasionally
2	Thyroid	Normal
H	CHEST	Normal
I	HEART AND PERIPHERAL VESSELS	
1	Heart	Normal
2	Rate and rhythm	Normal
3	Blood pressure	Normal or slightly increased, rarely excessive ^{38 43}
4	Peripheral arteries and veins	Normal
5	Vasomotor	Normal
J	BREASTS	
1	Male	Normal or slightly increased due to excess fat (see below)
2	Female	Often retarded in growth or prematurely developed tendency to atrophy in adults (see below)
K	ABDOMEN	
1	Liver	Normal unless metastatic lesions
2	Spleen	Normal

II OTHER TYPES—Excess androgenic steroid production by

- 1 Adrenal cortical tumors
- 2 Pheochromocytoma with cortical hyperplasia (rare)
- 3 Idiopathic
 - a Adrenal cortical hyperplasia
 - b Hypersecretion of adrenocorticotrophic hormone possibly
- 4 Accessory adrenal cortical tissue

X PATHOLOGY

A GROSS (see 39 I \ A)

- 1 Adrenal cortex^{70 71 72}
 - a Enlargement in both glands with out any other change
 - b Adenoma (found at autopsies with out any clinical evidence)
 - (1) Bilateral often
 - (2) Spherical
 - (3) Few millimeters to several centimeters
 - (4) Deep brown
 - (5) Capsule intact
 - c Adenocarcinoma
 - (1) Larger than adenomas
 - (2) Yellow
 - (3) Capsule often broken
 - (4) Soft
 - (5) Hemorrhage
 - (6) Necrosis
 - d Aberrant cortical rests may give rise to tumors indistinguishable from those found in adrenal cortex⁷³
- 2 Pituitary—normal⁷⁴
- 3 Thyroid—normal^{75 76}
- 4 Testes—variable⁶⁰
- 5 Ovaries—normal⁷⁷
- 6 Metastases to
 - a Brain
 - b Lungs
 - c Liver
 - d Opposite adrenal

III Microscopic

- 1 Adrenal^{70 71 72}
 - a Hyperplasia
 - (1) Adrenal cortices uniformly enlarged
 - (2) Hyperplasia may be
 - (a) Nodular
 - (b) Circumscribed
 - (3) Normal cellular structure

b Adenoma

- (1) Normal cells
- (2) Layers are not changed

c Adenocarcinoma

- (1) Cells
 - (a) Size—variable
 - (b) Shape—all kinds
 - (c) Nuclei—dark staining
 - (d) Undifferentiated
 - (e) Mitosis
- (2) Layers can be recognized in some areas
- d Adrenocortical rests—distinguishable from a group of Leydig cells by the connective tissue capsule

2 Other glands—normal

XI PATHOLOGIC PHYSIOLOGY

1 GENERAL

- 1 The bodily changes which occur in the adrenogenital syndromes are apparently due to hyperfunction of adrenocortical tissue (see 39 VI A 3)
- 2 The adrenogenital syndromes are caused chiefly by an excess production of androgenic hormones and as a rule are singularly free of abnormal effects from other adrenocortical hormones
 - a This is difficult to understand in cases where adrenal insufficiency and adrenocortical hyperplasia exist (see 39 \ C 2 a (3))^{78 79 80}
 - b The more recent opinion that one pituitary adrenocorticotrophic hormone is capable of stimulating three major (and theoretical) hormones of the adrenal cortex also complicates the problem an aberrant response is postulated⁸
- 3 The androgenic effects in the adrenogenital syndrome are chiefly as follows
 - a Muscle mass increases disproportionately although some cases show only accelerated
 - (1) Genital development
 - (2) Linear growth (see Fig 280 and Chart 94)
 - b Bone maturation is advanced
 - c Enlargement of clitoris or premature development of male genitalia and accessory organs
 - d Sexual and body hair are
 - (1) Increased
 - (2) Premature in appearance

b Glucose insulin	No data
c Insulin	Normal ⁶³
2 Adrenal water	Positive, if adrenal insufficiency supervenes ^{6 60}
3 Salt deprivation	No data
4 Balance	
a Nitrogen	Most likely positive to the extent found during growth
L MISCELLANEOUS TESTS	
1 Basal metabolic rate	Normal variation, occasionally elevated ^{7 26 34 40}
2 Circulation time	No data
3 Sedimentation rate	Normal
4 Specific dynamic action of protein	No data
5 Gastric analysis	No data
6 Electrocardiogram	Normal
F URINARY HORMONE ASSAYS	
1 FSH	Not increased ^{11 49}
2 LH	No data
3 Estrogens	Variable ^{6 12 16 23 28 37 40 46 49}
4 Pregnanediol	May be positive other derivatives have been found ^{13 14}
5 17 ketosteroids	Normal ^{4 7 9 11 22 26 33 34 37 40} or increased ^{46 1 53 55}
a Beta fraction	Increased more in tumors than with hyperplasia ^{6 54}
b Transdehydroandrosterone	Present with tumors only ⁹
6 11 oxysteroids	Normal or slightly elevated ^{11 53 6}
7 Aschheim Zondek	May be positive with tumor ³⁹
8 TSH	No data
G BIOPSY	
1 Endometrial	Atrophic probably
2 Testicular	No data
H VAGINAL SMEAR	Poor estrin effect
I SEMEN ANALYSIS	Little data, but spermatozooids reported present in a young male ^{7 1}

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL	
1 Cranial vault	Sutures may close prematurely
2 Sella turcica	Normal ³¹
3 Sinuses	Normal
4 Mandible	Normal
5 Teeth	Normal
B EPIPHYSEAL STATUS (bone age)	Increased ossification centers are advanced ^{7 20, 34 48 60}
C LONG BONES	Normal or denser than average
D VERTEBRAE	Normal
E BONE TEXTURE	Normal or decalcification is very slight
F MISCELLANEOUS	Normal

IX ETIOLOGY

A FETAL TYPE

- 1 Cause of adrenal cortical hyperplasia is unknown

- 2 It might be due to
 - a Transported or elaborated androgenic hormones by the placenta
 - b Abnormal stimulation from chorionic hormones (see 80 III)

C PSEUDOHERMAPHRODISM

- 1 Male—see 80 IV A and Table 74
- 2 Female—see 80 IV B and Table 73

XIV DIFFERENTIAL DIAGNOSIS

A CHILDREN

- 1 Granulosa cell tumor (females) (see 70 VII)
 - a Mental age—normal
 - b Contours—adult female
 - c Sexual hair—may be present
 - d Body hair—normal
 - e Breast development
 - f Clitoris—enlarged
 - g Vaginal bleeding
 - h Bone age—advanced in these cases also
 - i Demonstration of tumor by
 - (1) Palpation
 - (2) Laparotomy
- 2 Idiopathic or true sexual precocity
 - a Normal in all respects, except for premature development of puberty
 - b Masculinizing tendency is absent in female
 - c Body hair is not increased
 - d Clitoris is normal for sexual age
 - e Regular menstrual cycles with normal
 - (1) Ovulation
 - (2) Luteal phase
 - (3) Fertility

f Spermatogenesis and fertility in males

g No demonstrable

(1) Adrenal

(a) Hyperplasia

(b) Tumor

(2) Tumors

(a) Ovarian

(b) Testicular

(c) Pineal

3 Sexual precocity due to other causes

a Pinealoma (see 87 VIII)

(1) Headache

(2) Intracranial pressure signs

(3) Visual loss

(4) Ocular palsy or palsies

(5) Neurologic changes due to expansion and extension of tumor

(6) Confined to boys (rare exceptions)

b Cranial injury from disease, trauma or tumor

(1) History is important

(2) Any of these may duplicate true idiopathic sexual precocity

c Testicular tumor—see 54 X

4 Cushing's syndrome—see below

5 Pseudohermaphrodisism—see below and 80 IV A B

B ADULT (females)

1 Arrhenoblastoma (see 73 VI)

a Pelvic examination or exploration reveals tumor

TABLE 54 FEMALE PSEUDOHERMAPHRODISM OF ADRENOGENITAL TYPE⁴⁸

	OCCURRENCE		
	EARLY FETAL LIFE	LATE FETAL LIFE	AFTER BIRTH
Müllerian duct system	Retarded	Develops	Developed
Ovaries	Rudimentary	Rudimentary	Rudimentary
Vagina	Not visible	Visible may open into urethral hypospadias or calliculus seminales	Present
Breasts	Not developed	Not developed	Develop
Clitoris	Enlarged	Slightly enlarged	Enlarged
Hypopadias	Present	May be present (see above)	Absent
Prostate	Rudimentary	Absent	Absent
Masculinization	Present	Present	Present
Menses	Absent	Absent	Absent
Adrenal glands	Not enlarged	Not enlarged	Often very large may be 30 Gm or more glomerulosa and fasciculata zones increased may be in pelvis

- 4 Although masculinization occurs, excess of estrogens may be found in the urine
 - a This suggests that androgens are more successful in competing for the target organs than estrogens
 - b Experimental evidence, however, points to the probability that the response is a matter of concentration rather than a more selective advantage by either type of hormone
 - (1) During the growth period the penis responds readily to androgens, whereas after sexual maturity it changes very little or not at all
 - (2) The clitoris can increase in size at any time under the influence of androgens
 - (3) After sexual maturity, the female breasts do not increase from an excess of estrogen (pregnancy excepted)
 - (4) The growth of breasts is frequent in males especially after the opposing and potent androgens are eliminated by castration
 - (5) The target organs may respond equally to androgens or estrogens but experimental data favors the hypothesis that the pituitary is more sensitive to estrogens than androgens (see also inhibin 45 VI B 2)
 - c Urinary estrogen or androgen assays are not a measure of hormonal activity within the body, so that deductions from these may be misleading as to the physiologic activity of circulating hormones in the blood stream³⁰
- 5 The effects of excess androgenic secretion depend on the ability of target tissues to react — a phenomenon which is conditioned by
 - a The age of the organism (from embryo to old age)
 - b Other influences
 - (1) Disease
 - (2) Genetic defects (see above and Pseudohermaphroditism 80 IV True hermaphroditism 81 IV)

XII SYMPTOMATOLOGY

A ADRENOGENITAL SYNDROME

- 1 None usually
- 2 Physical and behavior changes are noted by parents
- 3 Pain with extension of malignant tumor
- 4 Marked strength
- 5 Voice deepens
- 6 Nocturnal emission in males
- 7 Vaginal bleeding in young females
- 8 Adrenal insufficiency develops in some at a later date

B VIRILISM OF ADRENAL ORIGIN

- 1 Change in psyche
- 2 Femininity lost
- 3 Weight decreased, if due to malignant tumor
- 4 Acne
- 5 Hirsutism
- 6 Recession of hair on temples (slight to marked)
- 7 Voice lower pitched
- 8 Amenorrhea

XIII DIAGNOSIS

A MALES

- 1 Young
 - a Precocious sexual development
 - b Testes usually small for body growth
 - c 17 ketosteroids — increased out of proportion to somatic development
 - d Bone age — advanced
 - e Adrenal tumor or hyperplasia may be demonstrated
- 2 Adults
 - a Feminization
 - b Testicular hypoplasia
 - c 17 ketosteroids and urinary estrogens are excessive
 - d Adrenal
 - (1) Tumor
 - (2) Hyperplasia

B FEMALES (young or adult)

- 1 Amenorrhea
- 2 Hirsutism — usually
- 3 Clitoris — large
- 4 17 ketosteroids — excessive
- 5 Bone age — advanced
- 6 Adrenal
 - a Tumor
 - b Hyperplasia

C. HORMONAL

1 Estrogens^{13, 41, 42}

- a Indication—girls with adrenal hyperplasia
- b Dosage (stilbestrol or other similar preparations), oral—0.2 to 0.5 mg daily (or more)

c. Results

- (1) Decrease in
 - (a) Acne
 - (b) Size of clitoris
- (2) Increase in
 - (a) Breasts
 - (b) Labia
 - (c) Female psyche

2 Progesterone

- a Indication—adjunct to estrogen therapy
- b Dosage oral (buccal)—30 mg daily for 5 days following 21 to 25 days of estrogens

c Results—as above

3 Cortisone^{43, 44}

- a Indication—males or females with adrenal hyperplasia
- b Dosage
 - (1) Infants—25 to 50 mg
 - (2) Older children
 - (a) Initially—50 to 100 mg
 - (b) Maintenance—10 to 25 mg

c. Results

- (1) Masculinization recedes
- (2) 17 ketosteroids decrease
- (3) Bone age retarded
- (4) Most favorable responses to date compared with other forms of treatment

XVII PROGNOSIS

A SUMMARY

- 1. Eventual outcome depends on pathology of adrenal
 - a Hyperplasia—may live normal life span
 - b Carcinoma—the following factors must be considered
 - (1) Duration of disease
 - (2) Presence of metastases
 - (3) Results of therapy (see above)
 - (a) Removal of all tumor cells
 - (b) Survival from possible post operative shock
 - c Adenoma—either course as above may be taken
- 2. Therapeutic result is an influencing factor

XVIII CAUSES OF DEATH

A ADRENAL INSUFFICIENCY

B POSTOPERATIVE SHOCK

C METASTASES⁴⁵

REFERENCES

- 1 Achard, C. and Thiers J. Diabetes of bearded women. *Bull Acad de med Paris* 86 51 66 1921
- 2 Bergman M. Sex precocity and the adrenogenital syndrome. *J Pediat* 31 142 153 (Feb) 1947
- 3 Blackman M. Jr. Concerning function and origin of reticular zone of adrenal cortex by periplasm in adrenogenital syndrome. *Bull Johns Hopkins Hosp* 78 180-217 (Apr) 1946
- 4 Broster L. R. Adrenals in sex Practitioner 158 307 314 (Apr) 1947
- 5 Butler A. M. Ross R. A. and Talbot N. B. Probable adrenal insufficiency in an infant. *J Pediat* 15 831 835 (Dec) 1939
- 6 Butler G. C. and Marrian G. F. Isolation of pregnane 3 17 20-triol from urine of women showing adrenogenital syndrome. *J Biol Chem* 119 562 572 (July) 1937
- 7 Cabill G. F. Melcown M. M. and Darby H. H. Adrenal cortical tumors: types of non hormonal and hormonal tumors. *Surg Gynec & Obst* 74 281 300 (Feb) 1942
- 8 Cecil H. L. Hypertension obesity virilism and pseudohermaphroditism as caused by suprarenal tumors. *J.A.M.A.* 100 463-466 (Feb) 1933
- 9 Crooke A. C. and Callow R. K. Differential diagnosis of forms of basophilism (Cushing's syndrome) particularly by estimation of urinary androgens. *Quart J Med* 8 233 249 (July) 1939
- 10 Darrow D. C. Congenital adrenal cortical insufficiency with virilism: case report. *Yale J Biol & Med* 16 9 538 (May) 1944
- 11 Escamilla R. F. Diagnostic significance of urinary hormonal assays: report of experience with measurements of 17 keto steroids and follicle stimulating hormone in the urine. *Ann Int Med* 30 249 260 (Feb) 1949
- 12 Fambblatt, H. M. Carcinoma of cortex of suprarenal gland with virilism: report of case with necropsy. *Arch Int Med* 88 469-4 3 (Oct) 1926
- 13 Finkler R. S. Pseudohermaphroditism. *M Woman's J* 53 31-42 (Oct) 1946
- 14 Forbes, A. P. Griswold G. C. and Albright F. Clinical experience with a bioassay method for the determination of urinary corticosteroids. *J Clin Endocrinol* 10 230-247 (Feb) 1950
- 15 Frank R. T. Suggested test for functional cor

- b Urinary androgens and 17 ketosteroids are excessive in either disease, but may be normal
- 2 Cushing's syndrome
 - a Masculinization is not as marked
 - b Buffalo type of obesity
 - c Striae are found in most cases
 - d Plethora
 - e Musculature not as well developed
 - f Clitoris is normal
 - g Diabetes may be discovered
 - h Bone age is most often delayed in prepubescent individual
 - 1 Osteoporosis is common
- 3 Hypertrichosis (female) (see Fig 282)
 - a Family history of hirsutism
 - b Menses—normal
 - c Virilism—absent
 - d 17 ketosteroids—may also be increased⁴⁴
- 4 Pseudohermaphroditism (see 80 IV A, B)^{48 49}
 - a Some cases of female variety are apparently of adrenal origin
 - b Anatomic abnormalities may depend on period of onset of adrenal cortical hyperfunction (see Table 54)
- c If no tumor is demonstrated
 - (1) Exploration is probably advisable
 - (2) Bilateral resection of the adrenals should not be attempted until both adrenals have been identified^{4 12 41 48}
 - (3) Some advocate removal of one whole adrenal, leaving other intact
 - (4) Since bilateral resection may be hazardous, this should not be undertaken unless condition warrants it and only by an experienced surgeon
- d Mild hyperplasia or small adenoma of adrenal do not require any operative procedure
- 2 Preparation of patient
 - a Special precaution should be taken to prevent adrenal insufficiency after operation although unlikely, it is possible (see 40 XVI E)
 - b Preoperative treatment with testosterone propionate (intramuscular)
 - (1) Indication—for anabolic effect to counteract catabolic phenomena during postoperative course (debatable)
 - (2) Dosage
 - (a) Intramuscular
 - [1] Adults—25 mg/24 hrs
 - [2] Children—1 mg/10 lbs body weight/24 hrs
 - (b) Duration—10 days before operation

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A COMPLICATIONS

- 1 None unless a malignant tumor is present
- 2 Social handicaps are obvious
- 3 Psychic trauma
- 4 Cardiovascular changes are extremely rare

B SEQUELAE

- 1 Metastases
- 2 Adrenal hemorrhage

C ASSOCIATED DISEASES

- 1 Cushing's syndrome
- 2 Pheochromocytoma
- 3 Adrenal insufficiency^{7 10 35 40}

XVI TREATMENT

A SURGICAL

- 1 Introduction
 - a Every effort should be made to establish presence or absence of a malignant tumor
 - b Duration of disorder may exclude possible malignancy in many cases

II ROENTGEN

- 1 Adrenal carcinoma—generally resistant to irradiation but advisable postoperatively
- 2 Inoperable cases—possibly some value
- 3 Hyperplasia—not beneficial

- Zygmuntowicz A and Wixom R Excretion of 11-oxycorticosteroid like substances by normal and abnormal subjects *J Clin Endocrinol* 7 331 350 (May) 1947
- 54 Talbot N H Butler A M and Berman R A Adrenal cortical hyperplasia with virilism diagnosis course and treatment *J Clin Investigation* 21 559 570 (Sept) 1942
- 55 Talbot N H and Butler A M Urinary 17 ketosteroids assays in clinical medicine *J Clin Endocrinol* 2 724 729 (Dec) 1942
- 56 Talbot, N H and Sobel E H Advances in Pediatrics, Interscience 1947 Vol 2 p 215
- 57 Thelander H E Congenital adrenal cortical insufficiency associated with macrogenitosomia follow up and terminal report *J Pediat* 29 213 221 (Aug) 1946
- 58 Wennberg T Contralateral adrenal atrophy associated with cortical adrenal neoplasm *New York State J Med* 41 884 885 (Apr) 1941
- 59 Wiesel, J Über accessorsche Nebennieren am Nebenhoden beim Menschen und über Compensations hypertrophie dieser Organe bei der Ratte Akademie der Wissenschaften (Sitzungsberichte der Mathematisch Naturwissenschaftlichen classe) 108 (Abt 3) 257 260 (May) 1899
- 60 Wilkins L, Fleischmann W, and Howard, J E Macrogenitosomia precox associated with hyperplasia of the androgenic tissue of the adrenal and death from cortico adrenal insufficiency *Endocrinology* 30 385 395 (Mar) 1940
- 61 Wilkins L and Richter C P A great craving for salt by a child with cortico adrenal insufficiency *J.A.M.A.* 114 866-868 (May) 1940
- 62 Wilkins L Lewis R A, Klein M, Gardner L I Cnigler J F Rosenberg E, Migeon C J Treatment of congenital adrenal hyperplasia with cortisone *J Clin Endocrinol* 11 1 15 (Jan) 1951
- 63 Wilkins L Gardner L I Cnigler Jr., J F Silverman S H and Migeon C J Treatment of congenital hyperplasia with cortisone I Comparison of oral and intramuscular administration, *J Clin Endocrinol.* 12 257 276 (Mar) 1952
- 64 ——— Treatment of congenital adrenal hyperplasia with cortisone II Effects on sexual and somatic development hypothesis *J Clin Endocrinol* 12 277 295 (Mar) 1952
- 65 Young H H Genital Abnormalities Hermaphroditism and Related Adrenal Diseases Baltimore Wilkins & Wilkins 1937 pp 234 239

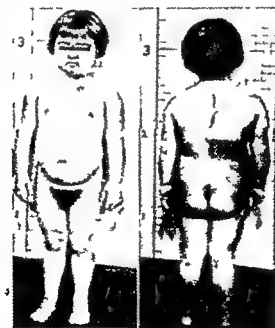


FIG 279 ADRENOGENITAL SYNDROME FROM ADRENOCORTICAL TUMOR Age 4½ female Note masculine configuration and swirls of hair (Meakins J C Practice of Medicine St Louis Mosby p 901 Photograph furnished by Dr Hector Mortimer)

- tical adrenal tumor *Proc Soc Exper Biol & Med* 31 1204 1206 (June) 1934
- 16 — Suggested test for cortical adrenal carcinoma *JAMA* 109 1121 (Oct) 1937
 - 17 Fraser I Precocious puberty in boy of one year *Brit J Surg* 27 521 526 (Jan) 1940
 - 18 Glynn E E The adrenal cortex its tests and tumours its relation to other ductless glands and especially to sex *Quart J Med* 5 157 197 1911 1912
 - 19 Goldschmidt quoted by Young H H Genital Abnormalities Hermaphroditism and Related Adrenal Diseases Baltimore Williams & Wilkins 1937 p 50
 - 20 Goldstein A E Rubin S W and Askin J A Carcinoma of adrenal cortex with adrenogenital syndrome in children *Am J Dis Child* 72 563 603 (Nov) 1946
 - 21 Gordon M B and Browder E J Suprarenal carcinoma with pubertas praecox in boy 3 years of age *Endocrinology* 11 265 278 (July Aug) 1927
 - 22 Hamblen E C Cuyler W K and Baptist M Urinary excretion of 17 ketosteroids in ovarian failure *J Clin Endocrinol* 1 63 771 (Sept) 1941
 - 23 Holmes G M A case of virilism associated with a suprarenal tumour recovery after its removal *Quart J Med* 18 143 152 (Jan) 1925
 - 24 Jacobziner H and Gorfinkel A Familial congenital adrenal syndrome *Am J Dis Child* 51 308 320 (Aug) 1936
 - 25 Jailer J W A fluorometric method for the clinical determination of estrone and estradiol *J Clin Endocrinol* 8 564 579 (July) 1948
 - 26 Johnson H T and Nesbit R M 17 ketosteroids in diagnosis of adrenal tumors *Surgery* 21 184 193 (Feb) 1947
 - 27 Klinefelter H F Jr Reifenstein E C, Jr., and Albright F Syndrome characterized by gynecomastia spermatogenesis without a Leydigism and increased excretion of follicle stimulating hormone *J Clin Endocrinol* 2 615 627 (Nov) 1942
 - 28 Koch F C Chemistry and biological significance of male sex hormones *J Urol* 41 199 205 (Feb) 1939
 - 29 Kolff W J and Tjotok A B Hirsutism and virilism in a 5 year old girl *J Clin Endocrinol* 10 270-279 (Feb) 1950
 - 30 Kenyon A T Adrenal cortical tumors—physiologic considerations *Surgery* 16 194 232 (Aug) 1944
 - 31 Kepler E J Kennedy R L J Davis A C Waters W and Wilder R M Suprarenal cortical syndrome and pituitary basophilism presentation of three new cases *Proc Staff Meet Mayo Clin* 9 169 181 (Mar) 1934
 - 32 Kepler E J and Keating F R Diseases of adrenal glands tumors of adrenal cortex diseases of adrenal medulla and allied disturbances *Arch Int Med* 68 1010 1036 (Nov) 1941
 - 33 Kepler E J., and Wilder R M Disturbances of carbohydrate metabolism observed in association with tumors of adrenal cortex *Acta med Scandinav (suppl)* 90 87 96 1938
 - 34 Levine S Z Butler A M Holt L E Jr and Weech A A Advances in Pediatrics New York Interscience 1947 pp 238 297
 - 35 Lewis, R A., and Wilkins L The effect of adrenocorticotrophic hormone in congenital adrenal hyperplasia with virilism and in Cushing's syndrome treated with methyl testosterone, *J Clin Investigation* 28 394-400 (Mar) 1949
 - 36 Lissner H Successful removal of adrenal cortical tumor causing sexual precocity in boy 5 years of age *Tr A Am Physicians* 48 224-235 1933
 - 37 Lukens F H W., and Palmer H D Adrenal cortical virilism *Endocrinology* 26 941 945 (June) 1940
 - 38 Marks T M., Thomas, J M and Warkany J Adrenocortical obesity in children *Am J Dis Child* 60 923 942 (Oct) 1940
 - 39 McCullagh E P., and Cuyler W K Positive Friedman tests in non pregnant states *Am J Clin Path* 10 591 602 (Sept) 1940
 - 40 McGavack T H Masculinizing and non masculinizing carcinomata of the cortex of the adrenal gland *Endocrinology* 26 356-408 (Mar) 1940
 - 41 McIntosh C B and Brown, W E. Adrenogenital pseudohermaphroditism treated with stilbestrol *J Pediat* 27 322 327 (Oct) 1945
 - 42 Mintz N and Geist S H Adrenal cortex in its relation to virilism *J Clin Endocrinol* 1 316 326 (Apr) 1941
 - 43 Neff F C Tice G M Walker G A and Ockerblad N Adrenal tumor in female infant with hypertrichosis hypertension overdevelopment of external genitalia obesity but absence of breast enlargement *J Clin Endocrinol* 2 125 127 (Feb) 1942
 - 44 Pedersen J The correlation between the degree of hair covering and the excretion of androgenous substances in the urine of normal women *Ugeskr Læger* 105 229 234 1943
 - 45 Pedersen A L A case of adrenal virilism presenting unchanged after excision of bilateral adrenocortical adenoma *Acta Endocrinol* 1 153 169 1948
 - 46 Pratt J P and Schaeffer H L Sex precocity virilism adrenal cortical tumor *Am J Dis Child* 49 623 633 (May) 1945
 - 47 Reifenstein E C Jr Forbes A P Albright F Donaldson E., and Carroll E Effect of methyltestosterone on urinary 17 keto steroids of adrenal origin *J Clin Investigation* 24 416-434 (July) 1945
 - 48 Reilly W A Lissner H and Hinman F Pseudo sexual precocity the adrenal cortical syndrome in preadolescent girls report of a successfully operated case *Endocrinology* 24 91 114 (Jan) 1939
 - 49 Saphir W., and Parker M L Adrenal virilism *JAMA* 107 1280-1288 (Oct) 1936
 - 50 Shephardson H C and Shapiro E Diabetes in bearded women (suprarenal tumor diabetes and hirsutism) clinical correlations of function of suprarenal cortex in carbohydrate metabolism *Endocrinology* 24 237 252 (Feb) 1939
 - 51 Soffer L J Clinical manifestations of adrenal cortical hyperfunction *New York Acad Med Bull* 23 4 9-493 (Aug) 1947
 - 52 Sprague R G Priestley J T., and Dockerty M II Diabetes mellitus without other endocrine manifestations in a case of tumor of the adrenal cortex *J Clin Endocrinol* 3 28 32 (Jan) 1943
 - 53 Talbot W H Albright, F., Saltzman A H



FIG 281 ADRENOGENITAL SYNDROME—CONGENITAL ADRENAL CORTICAL HYPERPLASIA

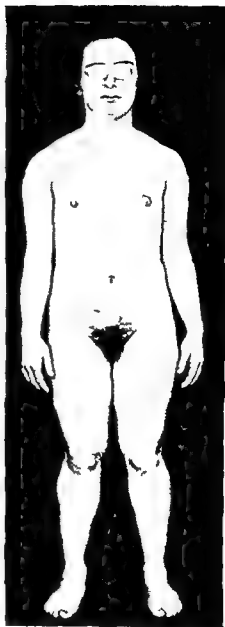
Chief Complaint Hirsutism

Family History Negative

Past History Patient born with enlarged clitoris. During past 2 years there has been excessive body and facial hair growth as well as appearance of pubic hair. Only 1 in of growth this past year. Excellent student.

Physical examination Age 13 years. Height 56 3/4 in. Weight 111 lbs. BP 138/78. Body configuration and other features as shown in photograph. Height age 11 years. Opening below clitoris probably urogenital sinus. Boogie entered bladder. Bimanual examination disclosed no uterus although this may be present.

Laboratory data Urine negative. Hgb 110% or 15.4 Gm. % RBC 5,515,000. WBC 7,900. Differential count normal. Total eosinophil count 13/cumm. Blood sugar 5 hrs p.c. 100 mg. % Serum phosphorus 2.8 mg. % 17 ketosteroids



51.2, 48.6 and 75.9 mg/24 hrs on 3 occasions. Beta steroid fraction 0. Urinary pregnandiol positive. Urinary 11 oxysteroids 0.189/100 cc.

Röntgenographic findings Skull normal. Radial epiphyses closed.

Treatment advised Cortisone 25 to 50 mg daily as advocated by Wilkins et al.⁶



FIG 280 ADRENOGENITAL SYNDROME
(See also Chart 94)

Chief complaint Precocity

Left

History of present illness Weight at birth 7 lbs 12 oz Onset at 1 year Walked at 14 months Recurrent tonsillitis and pneumonia Six year molars erupted at 3 years Perfectly well

Physical examination Age 3 Weight 45 lbs Height 43 in Height age 5 years

Laboratory data Blood count normal Eosinophils 6.5% Hinton negative Urinary 17 ketosteroids 14.6 mg/24 hrs

Röntgenographic findings Skull negative Sella 8 x 9 mm which is large for his age

Treatment None

Progress 2 years Weight 67 lbs Height 54 in Height age 11 years Adult size genitalia Body and axillary hair present

Right

5 years Weight 98 lbs Height 64 in Span 65½ in Pubic and axillary hair Body hair and fine facial lanugo Testes volume 5.5 to 8.5 cc Urinary 17 ketosteroids—total 54 mg/24 hrs alpha steroids 53 mg and beta steroids 100 mg Serum

phosphorus 4 mg % Total eosinophil count 38/cumm Bone age 1½ years 3 months Iliac crests open Patient in good health except for asthma in summer Morning erections occasional emissions

Comment Patient is intelligent in fourth grade and does very well He is not virile so to speak but rather timid and shy It is unlikely that this is a simple precocious development The excess of 17 ketosteroids is unusual and suggests an adrenocortical hyperplasia The low amount of beta steroids is against this Testicular biopsy would be helpful in that Leydig cells should be present if 17 ketosteroids are of testicular origin Final height should not be more than 66 or 67 in

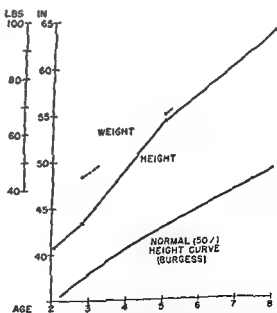


CHART 94 GROWTH CURVE OF BOY WITH
ADRENOGENITAL SYNDROME (See also Fig
280) Height age of 15 years at chronologic
age of 8 years

SECTION 43

FEMINIZING SYNDROME DUE TO MALIGNANT ADRENAL CORTICAL TUMOR

I DEFINITION

A syndrome characterized by development of the breasts in males, occasionally with lactation, and loss of sexual function, due to a malignant adrenal cortical tumor although suspected in some instances of being the result of an excess adrenal cortical function without tumor, this has not been proven⁴

II APPEARANCE

May gain weight and lose masculine facies

III AGE

Reported from 15 to 53 years, one case in a 5 year old boy¹

IV MENTAL DEVIATIONS

None or feminine psyche

V PHYSICAL STATUS

A INTEGUMENT

1 General

a Eruptions

Acne may develop

b Pigmentation

Face and abdominal linea fusca rarely^{1 4 6 14}

2 HAIR^{2 9 14 16}

a Beard

Less than usual

b Pubic

Decreased

c Body

May be lost

B BREASTS

Enlarged areolae well developed, superficial veins may be prominent milk or watery discharge may be expressed, tenderness sometimes^{1 2 7 8 10 14 16}

C ABDOMEN

1 Tumor

May be palpated

2 Liver

Normal or may be enlarged from metastatic lesions

D GENITALIA

1 Penis

Reduced in size

2 Testes

Soft and small^{8 9 10 14 16}

VI LABORATORY DATA

A GENERAL (urine hematology, blood chemical analyses)

Normal

B URINARY HORMONE ASSAYS

1 FSH

Negative or increased^{10 1}

2 Estrogens

Small or large amounts^{6 9 10 1}

3 17 ketosteroids

Slight increase, beta steroids may be increased^{10 14}

4 Aschheim Zondek

Negative in one case¹²

5 Friedman

Positive or negative^{2 8}

VII ROENTGENOGRAPHIC FINDINGS

A EPIPHYSEAL STATUS (bone age)

In Wilkins case 5 year old boy the bone age was advanced to 10 years, although the 17 ketosteroid excretion was not increased¹⁵



FIG 282 HYPERTRICHOISIS FOLLOWING SUBTOTAL THYROIDECTOMY FOR PRIMARY HYPERTHYROIDISM (See also Fig 172)

Family history Negative

Past medical Scarlet fever and tonsillitis

Chief complaints Nervousness palpitations and weight loss

History of present illness Patient has not been well for a period of 6 months. She has noticed a great deal of shortness of breath and palpitation on exertion.

Physical examination Age 17 Single Weight 96 lbs Pulse 140 BP 140/86 Skin warm and moist Thyroid small firm and symmetrically enlarged

Laboratory data BMR plus 31% and plus 21%

Diagnosis Primary hyperthyroidism

Treatment A subtotal thyroidectomy was done in 2 stages

Pathologic report Primary hyperplasia with irregular involution

Progress

MONTHS

12 Pulse 64 BMR minus 25% Feels fine

- 18 Complaints pain in right side of the abdomen and leg, chilliness, lethargy increased growth of hair on her face irregularity of periods and acne Adrenal tumor or basophilism was considered Improved on 1 gr of desiccated thyroid (USP) daily
- 24 Patient in well Periods normal Hair continued to grow
- 26 Bilateral adrenal exploration revealed nothing unusual Biopsy specimens from the adrenals were normal There was no change in hair growth
- 44 Patient stopped thyroid medication and myxedema returned Plasma cholesterol 358 mg %
- 46 Patient seemed better while taking desiccated thyroid Plasma cholesterol 169 mg %
- 32 Antutrin S given by her family physician with no improvement Mentally depressed No desiccated thyroid taken Hair about the same Roentgenogram of skull showed arteriosclerosis involving the left internal carotid

Follow up note Examined at Boston Dispensary for same complaints Growth of long hair particularly on the sides of her face and chin Male escutcheon Abundant hair on the extremities Clitoris normal

Laboratory data Normal urine complete blood count serum protein cholesterol sodium and chloride Glucose tolerance test normal BMR—minus 44% and minus 38% EKG—sinus arrhythmia Urinary androgens 200 which was considered normal

Roentgenographic findings Skull dorsal spine chest and adrenals revealed nothing abnormal

Diagnosis Unexplained hirsutism psychosis neurosis and hypothyroidism

Follow up note Patient died a year or so later in a mental institution No further data obtained

Comment As in so many cases of excessive hair growth no cause was determined. Postoperative myxedema may have stimulated hair growth but there was no regression on administering desiccated thyroid

XVI PROGNOSIS

A GENERAL

1 Good outlook

a If tumor can be completely extirpated

b Two cases recovered after successful removal of²³

(1) Adrenal tumor

(2) Adrenal rest tumor of testis

2 High incidence of malignancy in majority

XVII CAUSES OF DEATH

A METASTASES

GYNECOMASTIA AND TESTICULAR ATROPHY— Protocol XXXII Fig 283
A CASE ASSOCIATED WITH MIXED TUMOR OF RENAL ORIGIN

Family history Negative

Past medical Negative

History of present illness Enlargement of the breasts noted for 2 years Complained of pain in the back and right shoulder and loss of libido

Physical examination Age 38 male married Facial axillary and pubic hair normal Breasts enlarged with pigmented areolae Testes smaller than normal and soft. Prostate gland normal Large mass was felt in the right upper quadrant

Laboratory data Complete blood count and urine normal Urine FSH unsatisfactory twice blood FSH negative on admission Urine estrogens admission 2 plus 2 weeks later the same 3 weeks later 60 r u * Blood estrogens 1 plus on admission

Roentgenographic findings Chest normal Urograms—tumor mass pressing the right kidney down and anteriorly

Treatment Exploration revealed inoperable tumor involving liver Roentgen therapy produced only temporary recession in the palpable mass

Postmortem findings Testes—marked atrophy The tubules showed dense hyalinized basement membranes which were partially lined by a layer of polyhedral cells with shrunken hyperchromatic nuclei with a clear cytoplasm that was granulated and vacuolated Interstitial cells were decreased in number No evidence of spermatogenesis Prostate normal Liver—3 000 Gm Right lobe was largely replaced by a tumor which bulged through the capsule Areas of necrosis and hemorrhage as well as cystic degeneration were found There was yellow gelatinous fluid in the tumor The tumor mass itself weighed 1 900 Gm and extended anterior to and above the right

kidney and into the diaphragmatic hiatus Lungs and skull had metastatic nodules Pituitary and adrenal glands are normal grossly and microscopically Breast tissue was firm and measured about 9 cm in diameter Microscopic sections showed many branching ducts with small amounts of pink granular material in some Loose connective tissue stroma contained a few fibroblasts There were also some areas of dense collagenous tissue Arrangement was orderly and well defined basement membranes were present A rare mitotic figure was seen Several microscopic sections of the tumor were markedly necrotic with islands of viable tissue particularly about the vessels The cells were arranged in sheets in some places while in others there was an attempt at gland formation and long cords The tumor was quite vascular with very little stroma but where any intercellular tissue had been laid down it was loose The cell nuclei were rich in chromatin and had small round or oval nucleoli Cell membranes were not distinct the cytoplasm was scant light in color and contained vacuoles There were a few small groups of tumor cells growing along perineural lymphatics

Comment The presence of urinary estrogens in this case may have been due to inactivation of normal estrogens because of liver damage or may have originated in the tumor although none was found in extracts of the latter The gynecomastia may not have been related to estrogens but to factors similar to those causing it in Klinefelter's syndrome Although there was some decrease in Leydig cells beard growth continued to be heavy

Summary A case of gynecomastia associated with mixed tumor of renal origin with extensive metastases to the liver and testicular tubular atrophy

* Assayed by Drs G V S and O W Smith Fearing Research Lab Brookline Mass

VIII ETIOLOGY

A UNKNOWN

B ADRENAL TUMOR (see 39 IV A, 42 V)

C MIXED TUMOR—renal origin (see Protocol 43, VVVII)

IX PATHOLOGY

A GROSS AND MICROSCOPIC

1 Tumor

a Types

- (1) Malignant adrenal cortical tumor is most common
- (2) Mixed tumor of urogenital ridge⁶
- (3) Adrenal rest tumor of testis^{9 12}

b Characteristics¹⁵

- (1) Sharply outlined
- (2) Extension to
 - (a) Surrounding structures
 - (b) Liver
- (3) Calcification may be present
- (4) Cells
 - (a) Size—variable
 - (b) Shape—all kinds
 - (c) Nuclei—hyperchromatic
 - (d) Mitotic figures in malignant cases

2 Testes

- a Good spermatogenesis with few Leydig cells¹
- b Atrophic tubular tissue with few or absent Leydig cells^{6 10 11}

3 Breasts—typical histologic changes as those of a female lactating breast^{11 16} much periductal fibrous stroma in some¹⁵

X PATHOLOGIC PHYSIOLOGY

A SUMMARY

- 1 Changes are apparently due to
 - a Increased estrogens competing for end organ response
 - b Inhibition of pituitary gonadotropic hormones
- 2 Excess of urinary estrogens are not demonstrable in all cases

XI SYMPTOMATOLOGY

A GENERAL

- 1 Breasts
 - a Enlargement
 - b Tenderness
- 2 Hair—decreased

3 Sexual function—lost^{3 5 9 14}

4 Pain from tumor

XII DIAGNOSIS

A GENERAL

- 1 Gynecomastia
- 2 Genitalia—smaller than normal
- 3 Sexual hair—decreased
- 4 Abdominal mass may be
 - a Palpable
 - b Found in roentgenogram
- 5 Exploratory laparotomy may be required

XIII DIFFERENTIAL DIAGNOSIS

A GYNECOMASTIA

- 1 With aspermia (see 51)
 - a Condition present since puberty
 - b Potentia normal
- 2 Associated with
 - a Testicular tumors (see 54 IV B)
 - b Liver disease
 - c Other pathology—see 102 VI
 - d Idiopathic type (spermatogenesis present)
 - e Starvation

XIV COMPLICATIONS

A GENERAL

- 1 Metastases to^{3 15}
 - a Adjacent structures
 - b Kidneys
 - c Liver
 - d Spleen
 - e Lungs

B PAIN DUE TO MALIGNANT TUMOR

XV TREATMENT

A GENERAL

- 1 Surgical—removal of tumor if possible
- 2 Roentgen
 - a Tumor may be radiosensitive temporarily
 - b Postoperatively even if tumor is removed

B RESULTS

- 1 Enlargement of breasts
 - a Decreases⁹
 - b Disappears
- 2 Return of sex function even in those who ultimately succumb to metastases
- 3 Estrogens decrease in urine^{2 12}

SECTION 44

HYPERFUNCTION OF ADRENAL MEDULLARY OR OTHER CHROMAFFIN TISSUE DUE TO PHEOCHROMOCYTOMA

SYNONYMS

Paroxysmal or sustained hypertension Hyperepinephrinism
Hyperchromaffinism

I DEFINITION

A condition caused by excess secretion of epinephrine due to a chromaffin tumor of the adrenal medulla or accessory adrenal tissue and characterized by attacks of increased blood pressure which eventually becomes sustained (11%) few cases reported as asymptomatic and without hypertension¹¹

II APPEARANCE

As a rule nothing characteristic healthy appearance rarely adrenocortical features are present¹⁰

III AGE

Most frequently occurs between 20 and 50 ¹¹ youngest around 2 years⁸ and oldest 82 years¹⁸

IV SEX

Slight predominance of females

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal variations

B RESPONSIVENESS

Normal

C OTHER ABERRATIONS

May seem neurotic or confused · disoriented during attacks or late in disorder

VI PHYSICAL STATUS

A NUTRITION

Normal

1 Weight

Normal

2 Fat

Normal

B STATURE

Normal

C EXTREMITIES

1 Upper

Normal

a Hands

Normal

b Fingers

Normal

c Span

Normal

2 Lower

Normal

a Feet

Normal

b Toes

Normal

D SPINE

Normal

E INTEGUMENT

1 General

Normal

a Texture

Normal

b Temperature

May rise or fall during attack rectal temperature may rise

c Eruptions

None

d Pigmentation

None

e Color

Variable

REFERENCES

- 1 Buttorf, A. Nebennierentumor und Geschlechtsdrusenausfall beim Manne. *Berlin Klin Wchnschr* 56 776 (Aug) 1919
- 2 Cahill E F. Hormonal tumors of the adrenal. *Surgery* 15 233 265 (Aug) 1944
- 3 Chambers W L. Adrenal cortical carcinoma in a male with excess gonadotropin in urine. *J Clin Endocrinol* 9 451-456 (May) 1949
- 4 Glass S J and Bergman H C. Subclinical adrenogenital syndrome. *Endocrinology* 23 625 629 (Nov) 1938
- 5 Holl G. Zwei männliche Fälle von Nebennierenrindentumoren mit innersekretorischen Störungen. *Deutsche Ztschr f Chir* 226 277 297 (July) 1930
- 6 Hurxthal L M., and Musuhn N. Gynecomastia a case associated with mixed tumor of renal origin and testicular atrophy. *Labey Clin Bull* 4 38-44 (Oct) 1944
- 7 Luser H. Case of adrenal cortical tumor in adult male causing gynecomastia and lactation. *Endocrinology* 20 567 569 (July) 1936
- 8 McFadzean A J S. Feminization associated with carcinoma of adrenal cortex. *Lancet* 2 940 943 (Dec) 1946
- 9 Östergaard E. Feminizing tumor of the testis, presumably aberrant adrenocortical tumor. *J Clin Endocrinol* 7 438-445 (June) 1947
- 10 Robolm, K. and Teilmann G. Feminizing tumors of the suprarenal cortex with description of a case. *Acta med Scandinav* 3 190-211 1942
- 11 Selye, H. *Textbook of Endocrinology*. Acta Endocrinologica Montréal Université de Montréal 1947 p 171
- 12 Simpson J L., and Joll C A. Feminization in a male adult with carcinoma of the adrenal cortex. *Endocrinology* 22 595 604 (May) 1938
- 13 Soffer L J. *Diseases of the Adrenals*. Philadelphia Lea & Febiger 1946 p 222
- 14 Weber F P. A note on the causation of gynecomastia (mammary feminism). *Lancet* 1 1034 1035 (May) 1926
- 15 Williams L. Feminizing adrenal tumor causing gynecomastia in boy of five years contrasted with virilizing tumor in five year old girl. *J Clin Endocrinol* 8 111 132 (Feb) 1948
- 16 zum Busch J P. Gynakomastie bei Hypernephrom. *Deutsche med Wchnschr* 53 323 (Feb) 1927



FIG 283 GYNECOMASTIA TESTICULAR ATROPHY AND WILMS'S TUMOR OF RENAL (PRONEPHROS) ORIGIN (See also Protocol 43 XXXII) Age 38 Patient complained of enlarging breasts loss of libido and back ache Beard and body hair normal Abdominal mass Soft atrophic testes Urinary FSH negative Blood and urine estrin gave a positive reaction Androgens not determined Postmortem examination Tumor had long cords and acini of polyhedral cells Breasts—numerous clusters of branching ducts without acini Testes—marked atrophy of tubules but with Sertoli cells and decrease in Leydig cells (Hurxthal L M and Musuhn N. Gynecomastia A case associated with mixed tumor of renal origin and testicular atrophy. *Labey Clin Bull* 4 38 44)

K. ABDOMEN	
1 Liver	Normal unless congestive failure
2 Spleen	Normal
3 Hernia	None
4 Tumor	Palpable occasionally ⁶⁸
L. GENITALIA	
1 Male }	May be associated adrenogenital syndrome and secondary sex changes that are found with it
2 Female }	

VII LABORATORY DATA

A. URINE	
1 General	Output decreased and casts may be found during an attack.
2 Special analyses	
a Sugar	May be found continuously or only during attack ^{10 60 63}
b Albumin	Normal or present during an attack.
B. HEMATOLOGY	
1 Red blood cells	Normal
2 Hemoglobin	Normal or decreased
3 White blood cells	Normal or increased
4 Differential	Eosinophilia occasionally ⁶⁹ rarely eosinopenia ⁶⁰
C. BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal rises during attacks may remain high
2 Nonprotein nitrogen	Normal or increased especially during an attack or post operatively ^{11 60} up to 150 mg % has been reported ⁴⁷
a Urea	As for nonprotein nitrogen ⁶⁰
3 Protein	Normal
4 Uric acid	Normal or increased
5 Cholesterol	Normal or increased ^{8 11 76 48 63 66 68}
6 Sodium	Normal ^{11 63}
7 Potassium	Normal or increased rises with an attack ^{11 63} 33.5 mg % has been reported ¹¹
8 Calcium	Normal
9 Phosphorus	Normal ⁹
10 Phosphatase	Normal
11 Chlorides	Normal ⁶⁰
12 Iodine	Normal probably increased during attacks on account of adrenalin effect low total value ^{47 4}
13 Creatine	Normal ²⁸
14 Creatinine	Normal ⁶
15 Magnesium	No data
D. FUNCTION TESTS	
1 Tolerance	
a Glucose	Usually normal initial hyperglycemia or may show no rise 50 per cent may be diabetic possibly hypoglycemia after 4 to 6 hrs (or after an attack) (see 103 I J Chart 95 and Table 102 p 1426) ^{10 11 17 26 48 53 63 66}
b Glucose insulin	No data may be insulin sensitive
c Insulin	No data may be insulin sensitive
2 Adrenal water	Negative attack precipitated by ingestion of a large quantity of water ^{39 68}
3 Salt deprivation	No data

2 Hair	Normal, unless associated with adrenal cortical disorder as described below
■ Head	Plentiful, low browed, later recession develops
b Facial	May be increased in normal places as well as on neck, eyebrows may be thick and heavy
c Axillary	Normal
d Pubic	Increased, male distribution may be found in females
e Body	Normal or increased
F HEAD	
1 Shape and size	Normal
2 Facial expression	Apprehensive during attack
3 Eyes	
a General	Normal or possibly slight exophthalmos, pupils dilate during attack. lacrimation may occur ¹¹
b Fundi	Retinal changes of malignant hypertension may ensue, including choked disks ⁶¹
c Visual	
(1) Fields	Normal
(2) Acuity	May decrease with retinal changes
4 Ears and nose	May have angiospasm and blanching of tip of nose ¹¹
5 Mouth and throat	
a General	Normal
b Teeth	Normal
c Larynx	Normal
G NECK	
1 General	Normal or distension of neck veins
2 Thyroid	Normal
H CHEST	Normal or signs of pulmonary edema. respiration may increase during an attack
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal or enlarged and hypertrophied especially the left ventricle, as in hypertension. systolic murmurs
2 Rate and rhythm	Variable but usually increased during paroxysm. irregular or gallop rhythm may be found
3 Blood pressure	Persistent elevation of 20 to 30 per cent above 140/90, ^{1 6 11 13 14 1 7 47 9 63 0} with paroxysmal attacks, systolic may rise above 300 mm and diastolic over 160 mm ^{11 17 0 1 43 44 57 6 68 69} may have wavelike fluctuations during episodes, none of the attacks lasts less than 10 to 15 min, although symptoms may disappear before the blood pressure returns to its original level. postural hypotension ⁶⁴
4 Peripheral arteries and veins	Pulse variable but during attack very thin and at times not palpable because of intense vasoconstriction. oscillometric recordings may fail to demonstrate any peripheral pulse in severe spells. vessels may be sclerotic. postural tachycardia ⁶⁴
5 Vasomotor	Marked pallor and coldness of face and extremities are usually present in severe attacks. Raynaud's signs have been reported. ^a purplish blotching. face and scars may become cyanotic
J BREASTS	Normal

IX ETIOLOGY

A UNKNOWN

B FAMILIAL TENDENCY¹⁹X PATHOLOGY^{10 11 20}

A GROSS

1 Tumor

a Types

(1) Benign—largest percentage

(2) Malignant

(3) Diffuse hyperplasia

(4) Aberrant paragangliomas

b Location (see Fig 285)

(1) More common on right side

(2) Bilateral

(3) Aberrant tumors

(a) Retroperitoneal area²¹

(b) Sacrococcygeal region

(c) Along entire course of aorta

²²

(d) Carotid body

c Description

(1) Size—variable

(2) Encapsulated usually

(3) Consistency—solid or rather soft and cystic

(4) Cut surface

(a) Pinkish white

(b) Bright red

(c) Jellylike material

(d) Border may be yellow

(5) Many hemorrhagic areas and extravasation into peritoneum due to increased vascularity

(6) Necrotic and vacuolar degeneration are as common

(7) Cortical tissue may be

(a) Compressed

(b) Hyperplastic

d Metastases to

(1) Brain

(2) Neck

(3) Liver

2 Heart

a Enlarged

b Hypertrophied

3 Blood vessels are thickened

II MICROSCOPIC

1 Tumor (see Fig 286)

a. Cellular arrangement

(1) Alveolar

(2) Closely packed

(3) Sinusoidal

b Cells

(1) Size and shape are variable, but often

(a) Large

(b) Polyhedral (10 to 50 microns)

(c) Oval or round

(2) Nuclei

(a) Eccentric or centrally placed

(b) Oval or round

(c) Vesicular

(3) Cytoplasm

(a) Pale

(b) Granular—adrenalin may be demonstrated by stains¹¹

(c) Vacuolization often near sinusoids

(4) Few mitoses rarely malignant²²(5) Invasion of blood vessels suggesting possibility of benign metastasizing phenomena as in thyroid tumors¹¹2 Adrenal cortex—hyperplasia if adrenogenital or Cushing's syndrome is also present¹²

3 Thyroid may be replaced by fibrous or lymphoid tissue

4 Pancreas—hyperplasia of islets of Langerhans¹¹

5 Blood vessels

a Muscularis coat may increase

b Internal elastic lamina may be¹¹

(1) Thickened

(2) Ruptured

c Lumina narrowed

d Arterioles may reveal widespread necrosis¹²

6 Kidneys

a Thickening of glomerular capillaries

b Fibrosed Bowman's capsules

c Nephrosclerosis

C CHEMICAL ANALYSES

1 Tumors may contain¹²

a Epinephrine—to 2400 mg

b Nor-epinephrine—53 to 90 per cent²³2 Absence of^{27 28}

a. Fat

b Lipoids

c. Iron

3 Chromic salts turn tissues brown hence the name chromaffin

2 Hair	Normal, unless associated with adrenal cortical disorder as described below
a Head	Plentiful, low browed, later recession develops
b Facial	May be increased in normal places as well as on neck, eyebrows may be thick and heavy
■ Axillary	Normal
d Pubic	Increased, male distribution may be found in females
e Body	Normal or increased
F HEAD	
1 Shape and size	Normal
2 Facial expression	Apprehensive during attack
3 Eyes	
a General	Normal or possibly slight exophthalmos, pupils dilate during attack lacrimation may occur ¹¹
b Fundi	Retinal changes of malignant hypertension may ensue, including choked disks ⁶¹
c Visual	
(1) Fields	Normal
(2) Acuity	May decrease with retinal changes
4 Ears and nose	May have angiospasm and blanching of tip of nose ¹¹
5 Mouth and throat	
a General	Normal
b Teeth	Normal
■ Larynx	Normal
G NECK	
1 General	Normal or distension of neck veins
2 Thyroid	Normal
H CHEST	Normal or signs of pulmonary edema, respiration may increase during an attack
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal or enlarged and hypertrophied especially the left ventricle, as in hypertension systolic murmurs
2 Rate and rhythm	Variable but usually increased during paroxysm, irregular or gallop rhythm may be found
3 Blood pressure	Persistent elevation of 20 to 30 per cent above 140/90 ^{1 6 11 12 14 21 3 4 20 6 9} with paroxysmal attacks systolic may rise above 300 mm and diastolic over 160 mm ^{11 17 9 21 43 44 57 60 68 80} may have wavelike fluctuations during episodes none of the attacks lasts less than 10 to 15 min although symptoms may disappear before the blood pressure returns to its original level postural hypotension ⁶⁴
4 Peripheral arteries and veins	Pulse variable but during attack very thin and at times not palpable because of intense vasoconstriction oscillographic recordings may fail to demonstrate any peripheral pulse in severe spells vessels may be sclerotic postural tachycardia ⁶⁴
5 Vasomotor	Marked pallor and coldness of face and extremities are usually present in severe attacks Raynaud's signs have been reported ⁸ purplish blotching face and scars may become cyanotic
J BREASTS	Normal

- h Pain
 - (1) Epigastric¹⁶
 - (2) Precordial
- i Salivation may be excessive
- j Nausea
- k Vomiting
- l Diarrhea
- m Frequency
- n Anuria
- o Facial
 - (1) Pallor
 - (2) Flushing with circumoral pallor
- p Sweating
- q Tremors of
 - (1) Extremities
 - (2) Head
- r Leg cramps
- s Tinnitus
- t Mydriasis
- 4 Symptoms following attack
 - a None may feel well
 - b Lassitude
 - c Weakness
 - d Prostration
- B CHRONIC (when persistent hypertension present)
 - 1 Exacerbations may occur as described under acute paroxysms
 - 2 Symptoms associated with chronic hypertension
 - a Cerebral episodes
 - b Renal failure
 - c Paroxysmal dyspnea
 - d Angina of
 - (1) Effort
 - (2) Decubitus
 - 3 Weight loss
 - 4 Diabetes mellitus symptoms (if present)
- C FREQUENCY DURATION AND TIME OF ATTACKS^{21 22 23 24 25}
 - 1 Frequency
 - a Paroxysms eventually increase in number but years may pass between them
 - b Irregular intervals
 - c Death may occur with first attack
 - 2 Duration
 - a Dependent on amount and duration of epinephrine secretion
 - b Range—12 to 16 hrs
 - c It is hardly conceivable that the elevation of blood pressure would be

- less than 4 to 5 min although symptoms may last less than a minute
- 3 Time—any hour but more often during day
- 4 Pregnancy—attacks may be abated^{1 42}

XIII DIAGNOSIS^{1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25}

- A HISTORY—Paroxysmal episodes consistent with release of excess epinephrine
- B SYMPTOMATOLOGY
 - 1 Dizziness
 - 2 Headache
 - 3 Sweating
 - 4 Substernal pain
 - 5 Dyspnea
 - 6 Tremor
 - 7 Nausea
 - 8 Vomiting
- C PHYSICAL STATUS
 - 1 Blood pressure
 - a Fluctuates
 - b Remains elevated
 - c Increases during paroxysms
 - 2 Palpable tumor in either upper abdominal quadrant
 - 3 Fundi may show retinal changes of hypertension
 - 4 Signs of adrenocortical disturbance are rare
- D LABORATORY DATA
 - 1 Increase in
 - a Nonprotein nitrogen (blood)
 - b Urea (blood)
 - c Potassium (serum) especially during attacks
 - d Epinephrine (blood)
 - e Basal metabolic rate
 - 2 Perirenal insufflation by presacral route
- E SPECIAL TESTS (for methods see 39 XIII C 4)^{26 27 28}
 - 1 Repetition of acts which have been thought to incite a paroxysm or hypertension
 - 2 Massage of tumor produces a paroxysm
 - 3 Induction of paroxysm of hypertension by
 - a Adrenalin
 - b Histamine
 - c Etamon
 - d Mecholyl

4	Balance	
a	Nitrogen	No data
5	Renal	
a	Phenolsulfonphthalein	Normal ⁶³
b	Urea clearance	Variable ^{11 35}
E	MISCELLANEOUS TESTS	
1	Basal metabolic rate	May be increased in continuously secreting tumors or during an attack. (see Chart 96) ^{8 9 19 2}
2	Circulation time	No data but should be increased
3	Sedimentation rate	Normal ¹¹
4	Specific dynamic action of protein	No data
5	Gastric analysis	Normal or decreased ³⁹
6	Electrocardiogram	May change during an attack with S T elevation or depression, T and P waves high, various other abnormalities as found in hypertensive cases, i.e., left ventricular strain patterns ^{11 47 68}
7	Total base	Normal ⁶⁵
F	URINARY HORMONE ASSAYS	
1	FSH	Normal probably ⁴⁰
2	LH	No data
3	Estrogens	Normal probably ⁴⁰
4	Pregnandiol	No data
5	17 ketosteroids	Normal, ⁶⁹ may increase after an attack ⁴
6	11 oxysteroids	Normal ^{11 69} or slight increase ⁴⁰
7	Aschheim Zondek	Negative ¹⁰
8	TSH	No data
9	Epinephrine (or nor epinephrine)	Increased ²² normal or increased in the blood especially during attacks ^{6 61}
G	BIOPSY	
1	Endometrial	No data, but normal probably
2	Testicular	No data but normal probably
H	VAGINAL SMLAR	Normal
I	SEMEN ANALYSIS	Normal
VIII ROENTGENOGRAPHIC FINDINGS		
A	SKULL	Negative ¹¹
B	EPIPHYSEAL STATUS (bone age)	Normal unless associated with adrenocortical disorders
C	LONG BONES	Normal
D	VERTEBRAE	Normal
E	BONE TEXTURE	Normal
F	MISCELLANEOUS	Tumor may be large enough for demonstration by pyelograms perirenal insufflation or flat plate of abdomen calcified in some rarely shown in chest ⁴⁹ 12 per cent of tumors outside adrenal area (see Fig 284) ⁴⁹

- Alcoholic persons fatty liver in acute hepatic insufficiency in 738
clinical manifestations of 505-506
effects of therapy on 507
laboratory findings in 506-507
structural alterations in 507
- Alcoholism modifying clinical course of hepatitis 424
in parallel involvement of pancreas and liver 633
- Aldolase 733
- Aldosterone 294 295 638
- Alkaline phosphatase 49
Alkaline phosphatase 11 46-47
92 213 217 237-239
in biliary obstruction 47
in butter yellow intoxication 47
in carbon tetrachloride intoxication 47
chemical differences in 47
cytologic demonstration of 47
function of 48
in hepatic damage 47
histochemical demonstration of 48
immunologic differences in 47
in necrotic cells in subacute yellow atrophy and cirrhosis 47
normal distribution of in bile canaliculi 47
in ducts 47
in ductules 47
in hepatic cell 47
after partial hepatectomy 47
after protein depletion 47
sites of 48
species differences in 47
in subacute hepatitis 47
types of hepatic 48
intestinal 48
serum (see Serum alkaline phosphatase)
- Alkaloids conjugation of with glucuronates 68
- Alkalosis respiratory in hepatic coma 735
- Allantoin 45
- Allergic reactions in liver 658
in viral hepatitis 658
- Allergy effect of liver upon 658
experimental 658
human hepatic reactions in 658
- Alloxan diabetogenesis 640
- Allyl formate 396 398
- Alpha₁ fraction 42 317
- Alpha fraction 42 317
- Alpha₁ globulin 323
- Alpha globulin 42-43 216 282 317
alpha₁ fraction in 42
alpha fraction in 42
in hepatectomized animals 43
in liver disease 43
after partial hepatectomy 43
serum level of 319
- Alpha ketoglutarate 25 215
removal of from Krebs cycle in brain 223
- Alpha ketoglutaric acid 26
- Alpha methene bridge 75
- Alpha naphthylthioarea (ANTU) 196
- Alveolar echinococcus 576 578
- Amanita phalloides 400
- Amanita toxin 400
- Amebiasis hepatic 569-571
incidence of 569
life cycle of 569
therapy in 571
- Amebic abscess of liver 570-571
clinical manifestations of 570
laboratory findings in 570-571
structural alterations in 571
- Amebic enteritis hepatomegaly during 569
- Amebic hepatitis acute 569-570
clinical manifestations of 570
laboratory findings in 570
structural alterations in 570
- Amination 26
- Amino acid oxidase 26 51
- Amino acid-tolerance tests 339
evaluation of 339
intravenous tests with amino acid mixtures 339
methionine tolerance tests 339
oral tests 339
physiologic basis of 339
- Amino acids 26 40-41 218
antiketogenic or glycogenic 28
in bile 81
conjugation with 67-68
dicarboxylic 28
essential 26
hepatic 40-41
ketogenic 28
lipotropic 38
polypeptide binding of 27
in portal vein blood 41
release of 44-45
in hepatocellular degeneration 44
serum 337
specific deficiency of 495-496
total in blood and urine 337-338
urinary (see Urinary amino acids)
- Amino nitrogen 217
- Aminocetic acid 27
(See also Glycine)
- Aminocidemia 48
- Aminoaciduria 45 541-542
- Aminocystine 593
- Amitotic division 83
- Ammonia 26
in liver 27
metabolism of 27
in urea 27
- Ammonia transport mechanism 223
- Ammoniacal encephalopathy 224
- Ammonium sulfate half saturated solution of 316
- Ampulla 103 108
intrinsic muscles of 109
variations of 108
- Amylase 50 633
in bile 81
determination of 343
in liver disease 50
- Amyloid 11
- Amyloidosis 545-547
pathogenesis of 545-547
primary 545-546
features of 547
secondary 545
clinical and laboratory findings in 546-547
structural alterations in 547
histologic changes 547
macroscopic appearance 547
- Anaerobic bacteria 143
in livers 99
- Anaphylactic shock 147
- Anastomoses portohepatic venous 272
portosystemic (see Portosystemic anastomoses)
vascular 262 274 277-278
functional significance of 277
hepatic artery-portal vein communications in 277-278
- Androgens in bile 81
- Anemia in experimental liver damage 628
hemolytic 99 488
in hepatic diseases 628
macrocytic 628
pernicious 629
role of in secondary hemochromatosis associated with anemia 540
sickle-cell (see Sickle-cell anemia)
- Anemic infarcts 143-145
- Anesthetics 401
choice of in patients with liver disease 401
- Aneurysms of hepatic arteries 145 581
clinical manifestations of 581
etiology of 581
treatment of 581
- Angitis hypersensitivity 581
- Angiogenesis 277 528
- Angiomatosis diffuse hepatic 591
- Animals nutritional hepatic injury in 493-496
viral hepatitis in 456-457
(See also Tests in animal experiments)
- Antigen bile canaliculi 165
bile secretion 165
common ducts 165
cystic duct 165
extrahepatic bile ducts 165
gallbladder 165
hepatic diverticulum 165
omphalomesenteric veins 165
organizers 165
septum transversum 165
vitelline veins 165
- Anorexia 219 630
biliary pressure causing 113
- Anoxia 59 82 203
and regeneration 93
- Anoxic necrosis 143 213
- Anterior pituitary extracts 30 635
- Anthraxene 6-65
- Antibiotic treatment in acute viral hepatitis 426
- Antilotics 402 735
in bile 81

XI PATHOLOGIC PHYSIOLOGY

A GENERAL

- 1 The initial abnormal changes which occur in the body from a chromophil tissue tumor are entirely due to an excess of circulating epinephrine and/or nor epinephrine
- 2 All symptoms or signs observed in a typical paroxysmal attack have been noted from an excess administration of the epinephrine in either animals or man (see also 39 VI B 2)
- 3 It seems likely that stimulation of sympathetic nerves ending in the tumor cause discharge of accumulated epinephrine within the cells
- 4 In cases with persistent elevation of blood pressure, a vicious circle suggests itself
 - a The continuous excess of epinephrine stimulates the sympathetics which, in turn cause the tumor cells to discharge their hormone
 - b It is doubtful if the mechanism is as simple
- 5 The occurrence of diabetes* 30
 - a Its cure following removal of the tumor suggests the possible elaboration of carbohydrate hormones by the cortex
 - b Epinephrine may cause release of adrenocorticotropin which in turn stimulates the cortical hormones
 - c The increased bodily metabolism due to excess epinephrine as well as its action on the whole carbohydrate mechanism may indicate the exacerbation of a latent diabetes in some cases
- 6 Death from an excess of epinephrine or nor epinephrine in man may be similar to that in animals^{31 37}
 - a Excitement followed by depression
 - b Heart rate is very rapid
 - Respirations—increased
 - d Muscular paralysis may develop
 - Asphyxial convulsions
 - f Multiple hemorrhages throughout the body
 - g Cardiac dilatation
 - h Pulmonary edema due to left heart failure

XII SYMPTOMATOLOGY

A ACUTE

- 1 No complaints in 11 per cent of cases¹¹
- 2 Precipitating factors—discoverable in 50 per cent may occur during sleep
 - a Pain
 - b Exercise
 - c Hyperventilation
 - d Emotion
 - e Sneezing
 - f Excess intake of
 - (1) Food
 - (2) Fluids
 - g Position
 - (1) Lying on side of tumor
 - (2) Bending forward or backward
 - h Labor
 - i Menses
 - j Carotid sinus pressure⁴⁰
 - k Anesthesia⁴¹
 - l Surgical operations
 - m Tumor, direct
 - (1) Palpation
 - (2) Massage
 - n Cold pressor test (see 39 VIII C 4 c)
 - o Injection of (see 39 VIII C 4 a, b)
 - (1) Histamine⁴²
 - (2) Mecholyl
 - (3) Etamon⁴⁶
 - (4) Adrenalin (1 to 2 mg) (may be hyposensitive)^{8 19 47 50 51}
 - (5) Cocaine
- 3 Symptoms during paroxysm
 - a Peculiar feelings that are difficult for patient to describe and which might be considered functional i.e. an anxiety state or neurosis
 - (1) Sinking sensation in abdomen
 - (2) Apprehension often severe
 - (3) Dizziness
 - (4) Choking
 - b Headache
 - (1) Pounding
 - (2) Expanding
 - c Breathing
 - (1) Dyspnea
 - (2) Hyperventilation with tetany
 - d Palpitations
 - Chest
 - (1) Pressure
 - (2) Constriction
 - f Cough
 - g Hemoptysis

- Benzene 68
 (See also Halogenated benzenes)
 Benzoic acid 67 68
 Benzoyl 68
 Benzoyl glucuronate excretion de-
 termination of 369-370
 cinnamic acid test 369
 method of 369
 physiologic basis of 369
 results of 369-370
 Berylliosis 559
 Beryllium sulfate 396 736
 Best's carmine stain 11
 Beta carotene 52
 Beta globulin 43 317
 in hyperlipemias 43
 iron binding globulins in 43
 lipoproteins in 43
 in obstructive jaundice 43
 in parenchymal liver diseases 43
 serum level of 319
 in xanthomatous biliary cirrho-
 sis 319
 Beta glucuronidase 50
 Beta hydroxybutyric acid 25 28
 Beta oxidation 25
 Betaine 38
 Betaine transmethylese 50
 Bianchi 390
 Bicarbonate in bile 81
 Bile 80 299
 A 377
 abnormal 84
 in absorption of fat 734
 alteration of 300
 antibiotics in 81
 B 377
 bacteriology of 81-82
 bile acids in 81
 bile pigments in 81
 in body salt 84
 C 377
 in carbon tetrachloride intoxi-
 cation 84
 in choline deficient fatty livers
 84
 color of 80
 drugs in 81
 effect of on carcinoma forma-
 tion 304
 enzymes in 81
 exogenous substances in 81
 flow of (see Bile flow)
 formation of (see Bile forma-
 tion)
 freezing point of 80
 function of 84
 gallbladder 80
 hepatic 80-81
 human bacteria in 81
 inspection of 378
 limey 301
 liver chemical constitution of 81
 water content in 81
 milk of calcium 116 301
 pH of 80
 physical characteristics of 80-81
 prolonged absence of 84
 secretion of (see Bile secretion)
 specific gravity of 80
 therapeutic value of 84-85
 in biliary dyskinesia 85
 effect upon intestine improved
 absorption 84
 laxative action 84
 increase of bile flow 84
 after relief of biliary obstruc-
 tion 84
 typhoid bacillus in 82
 vitamins in 81
 volume of 80
 in water balance of body 84
 white 84
 Bile acid metabolism abnormali-
 ties of 65
 tests based on 365-366
 Bile acids 27 237 307
 administration of in hepatic
 damage 85
 in obstructed common ducts
 85
 artificial 63-64
 in bile 81
 and feces 366
 chemistry of 63-64
 in cholestasis 65
 from cholesterol 36-37
 amount of 36
 form of 36
 origin of 36
 relation of to blood level 37
 conjugated 63 64
 effect of on serum cholesterol
 36
 emulsifying effects of 299
 formation of in hepatectomized
 dog 64
 in hepatic infection or biliary
 obstruction 64
 forms of 64
 function of 65-66
 absorption of calcium iron
 and copper 66
 absorption of some steroids
 66
 activation of enzymes 65
 antirachitic action of bile salts
 65-66
 bacteriostatic action 66
 as choleretics 66
 emulsifying or surface tension
 action 65
 hydrotropic action 65
 laxative effect 66
 water retaining power of bile
 salts 66
 glycocholate 63
 during hydrocholeresis 83
 injection of 64
 in phagocytosis 98
 physiologic loss of 64-65
 role of in urinary excretion of
 bilirubin 78
 serum 365
 species variations in 63
 storage of 65
 toxicity of affecting renal epi-
 thelium 66
 affecting wall of gallbladder
 66
 anticoagulant effect of 66
 inactivation of cholinesterase
 as effect of 66
 Bile acids toxicity of metabolic
 effect of 66
 producing gastric ulcers 66
 specific hemolytic effect of 66
 in urine 64-65
 determination of 365-366
 by Hays test 365
 by Pettenkofer reaction
 365
 by straggometry 365
 Bile canaliculi 103 165
 diverticula of 103
 obstruction of 184
 rupture of 183
 and tissue spaces: communica-
 tions between 182
 Bile canaliculus drainage func-
 tional interference with 185
 Bile canaliculus stains 11
 Bile capillaries (see Bile cana-
 culi)
 Bile casts 183-184 193
 in hepatic cell damage 183
 in severe hepatic injury 183
 Bile duct anastomoses 106
 Bile duct dilatation 232 235
 Bile ducts 90
 aberrant in gallbladder 112
 accessory 171
 common (see Common bile
 duct)
 development of 165-166
 structural organizers in 166
 extrahepatic (see Extrahepatic
 bile ducts)
 interlobular 120-121
 intrahepatic (see Intrahepatic
 bile ducts)
 large 121
 obstruction of 184
 and pancreatic duct relationship
 of 632
 proliferating 90 92
 regeneration of 120-121
 septal 103
 smallest obstruction of 184
 vestigial 106
 Bile ductules 103-106
 regeneration of 119-120
 Bile extravasates 235
 Bile extravasation 225
 Bile fistula 64
 Bile flow functional interference
 with 184
 hepatic reflex inhibition of 83
 mechanical interference with
 184
 Bile formation 80-85
 factors influencing 82-83
 bile acids 82-83
 circulation 82
 diet 83
 diurnal variations 83
 drugs 83
 filtration vs secretion 82
 hormones 83
 nervous regulation 83
 paralysis of 184
 Bile infarct 232
 Bile lakes 188 225 227
 intralobular 229
 Bile phospholipids 34
 Bile pigment deposition 20

- A fibroes bacterial production
 of in cirrhosis 99
 in hepatitis 99
 formation of during blackad
 101
 by Kupffer cell 99
 specific in hepatitis 99
 Anticonulsants 402
 Antigen antibody complexes in
 Kupffer cells 99
 Antigens in Kupffer cells 99
 Antilipoptone 39
 Antimony 401
 Antithrombin 337
 Antituberculous drugs 402
 Aplasia 286
 complete 171
 congenital of ducts 193
 Apoferritin 20 44 59
 Aqueous humor of eye bilirubin
 in 198
 Arginase 27 48 50
 Arginine 27
 urinary excretion of 45
 Arsenical cholangiolitis 403
 Arsenicals 196 229 400-401
 Arsenocholine hypotrophic activity
 of 39
 Arsenic 179
 Arterial blood supply increased
 in portal hypertension 294
 Arterial emboli 145
 Arterial pressure 82
 Arterialization of portal vein 142-
 143
 Arteriovenous fistulas 127
 hepatoportal 288
 Arteriovenous oxygen difference
 739
 in cirrhosis 294
 Artery cystic 122
 variations of 122
 gastroduodenal 122
 hepatic (see Hepatic artery)
 internal mammary 125
 left gastric 122
 phenic 125
 hepatic artery with anastomoses
 of 125
 renal 125
 right gastric 122
 right gastroepiploic 122
 splenic 122
 superior pancreaticoduodenal
 122
 supraduodenal 122
 supraceliac 125
 Arthritis 65
 hematoid joint and liver
 disease 65
 Atrophied in liver 578
 Atrial 246
 Ascaris 193 568
 Ascaris extract 147
 Ascaris lumbricoides 572
 Aschoff 97 179
 Ascites 21 92-297
 altered renal function in 294
 s contraindication for venous
 shunt operation 92
 excess hormones in 294-295
 after experimental cirrhosis 286
 Ascites experimentally produced
 292-293
 chronic hepatic injury 292
 constriction of abdominal veins
 cava and portal vein 293
 passive congestion 292-293
 from gradual ligation of portal
 vein 141
 in heart failure 295
 in hemorrhage 292
 in liver proteinemia 294
 increased capillary permeability
 1 295
 in increased hepatic lymph pro-
 duction 295
 ter ligation of factors in 295
 lymphatic changes in 295
 pathogenesis of 293-295
 in portal lymphatic obstruction
 in 295
 in portal hypertension 294
 rate of formation of 292
 sequelae of 295-296
 adhesions 296
 changes in blood volume 296
 circulatory embarrassment
 295
 disturbed renal function 296
 edema formation 295-296
 liver proteinemia 296
 interference with intestinal
 absorption 296
 respiratory embarrassment 296
 sodium retention in 294-295
 therapy for 296-297
 high protein diets 296-297
 mercurial diuretics 296
 paracentesis 296
 peritoneal therapy for 297
 sodium restriction 296
 Ascitic fluid bilirubin in 193
 circulation of proteins in 293
 cultivation of water in 293
 hemorrhagic in cirrhosis 221
 protein content of 293
 Ascitic fluid pressure 293
 Asparagus 223
 Aspartic acid 26 27
 urinary excretion of 45
 Aspiration of hemangiom of
 liver 739
 Aspiration biopsy 331
 At brine 199 401
 Atabrine 199
 Athetosis in liver disease 651
 ATP (adenosine triphosphate) 25
 7 30
 effect of irradiation on 657
 in mitochondria 21
 Atresia 170 171
 clinical features of 171
 congenital of bile duct 193
 surgery for 171
 treatment of 171
 xanthomatous stage of 171
 Atrophy 205
 acute yellow (see Acute yellow
 atrophy)
 brown 19 205
 cyanotic 477
 fatal 205
 hereditary of Goodpasture
 268
 Atrophy internal pressure 205
 of left lobe of liver 205 266
 renal 205
 red 212
 reticular 644
 from undernutrition 205
 Atropine 147
 Autointoxication 223
 Autohysis 45 173
 Autopsy specimens histological
 alterations in 408 411
 Avascular oxygen difference hepatic
 145-146
 in cirrhosis 146
 A vein 401
 Axillary hair 644
 Azo dyes 593
 Azorubin S dye 85 86 647
 Azorubin M test 373
 Azotemia 649
 cause of in hepatic disease 650
 in experimental animals 650
 B
 Bile 377
 B virus 414
 and A virus cross immunity be-
 tween 417
 differences between 416
 immunity after 417
 B virus hepatitis and A virus hepa-
 titis clinical differences be-
 tween 422-423
 epidemiology of 419-421
 parental transmission of types
 of 419
 (See also Hepatitis serum)
 Bacteremia 735
 Bacteria anaerobic 99 143
 as cause of intrahepatic cholan-
 giasis 196
 in cholecystitis 307
 routes of invasion of 307
 in human bile 81
 intestinal 223
 in liver 99
 splenic removal ratio of 99
 Bacterial endocarditis subacute
 145
 hepatic changes in 407
 Bacterial hepatitis 407
 Bacterial infection 235
 Bacteroides 246
 BAL 54
 Balantidium coli 57
 Bant's 289
 Bant's syndrome 239 290 6-3
 Bant's test in liver disease 69
 Banum sulfate turbidity standard
 324
 poccur in 324
 reagents for 324
 technique of 324
 Bile 54
 sophisticated and cholesterol-deficient
 diet 16
 loss of 202
 of nuclei and DNA 21
 and nuclear size 16
 Basophilic granules (see PAN
 granules)
 Belch's 219

- Biopsy needle 380-381
 biopsy sites for 380
 needles for 380
 aspiration needles 380
 Franseen 380
 Iversen Roholm 380
 Roth Turkel 380
 punch needles 380
 Vim Silverman 380
 technique for 380
 nonfatal complications in 382-383
 peritoneoscopic 379-380
 punch 381
 and results of therapy 384
 in sarcoidosis 557
 specific problems studied with 383-385
 surgical 379
 and tests application of as an
 illary procedures in clinical
 problems 664-669
 in tuberculosis 739
 when to do 453
 Biopsy examination focal lesions
 found by 384
 Biopsy findings in hemochromatosis
 536-538
 in hyperthyroidism 485
 Biopsy specimens 418 626
 cirrhosis in 529 530
 depositions in liver recognized in
 384
 fatty liver 384
 incidence of hepatic sarcoidosis
 in 557 558
 of nutritional fatty liver with
 hepatocellular degeneration
 508-510
 of postnecrotic cirrhosis 451
 452
 structural changes in 408
 of tuberculosis 553
 Botulin 38, 58
 Bismuth therapy 401
 Biuret reaction 315
 Biuret reagent 315
 Blastema formation of 92
 regeneration forming 90
 Blastomycosis 567
 Blockade 101-102
 antibody formation during 101
 bile pigment metabolism during
 101
 phagocytosis during 101
 Blood administration of in exogenous
 siderosis 534
 composition of differences in
 various vessels 145-146
 partial obstruction of more
 than one vessel 146
 urobilinogen in 78
 Blood ammonia level 27
 and hepatic coma 735
 Blood and bile pigment metabolism
 70-79
 Blood cells phagocytosis of 99
 Blood cholate level in biliary obstruction
 65
 in experimental hepatic damage
 65
 in human acute hepatitis 65
 after injection of cholate 65
 Blood content variations in in
 biopsy specimens 174
 Blood depot 147
 Blood dyscrasias 565
 Blood flow, average 137
 hepatic (see Hepatic blood flow)
 hepatic artery 143-145
 through periphery of liver 140
 portal (see Portal blood flow)
 reversed in portal vein branches
 in portal hypertension 184
 within sinusoids 735
 Blood flukes (see Schistosomiasis)
 Blood glucose determination of
 344
 Blood pigment breakdown Kupfer
 cells in 101
 Blood pressure in large hepatic
 veins 145
 Blood products processed in viral
 hepatitis 420
 Blood pyruvate level 219
 Blood sugar 30 31
 disturbed release of in liver
 disease 31
 formation of rate of 31
 source of 31
 Blood sugar level 31 219 344
 Blood sugar portal vein 30
 Blood transfusions 399
 role of in secondary hemochromatosis
 associated with an
 emia 539
 Blood urea level 27 217 218 338
 Blood urea nitrogen (BUN), 218
 Blood vessels (see Hepatic blood
 vessels)
 Blood volume changes in as sequelae
 of ascites 296
 Bodansky method of serum alkaline
 phosphatase technique
 for 340
 calculations in 340
 procedure in 340
 reagents in 340
 Body fluids bilirubin in 198
 Bollman 218
 Bone marrow alteration of 628
 replacement of in postnatal
 hematopoiesis 624
 Botulinus toxin 398
 Borden - minute pause of 115
 118
 Bradycardia 66 219
 in jaundice 651
 Brain influence of on liver in
 anxiety states 653
 in multiple sclerosis 653
 in schizophrenia 653
 in toxic psychosis 653
 influence of liver on 652-653
 Brain changes morphologic in
 hepatic injury 652
 Bromobenzene 38 396
 detoxification of 69
 percutaneous administration of
 producing hepatic necrosis 69
 Bromsulphalein (BSI) 85 86
 370 647
 biliary excretion of 372-373
 in extrahepatic uptake or hepatic
 destruction 85
 in hepatectomized animals 85
 Bromsulphalein for hepatic blood
 flow 137
 hepatic clearance or extraction of
 372
 injected 237
 radioactive enterohepatic circulation
 of 85-86
 urinary excretion of 85
 Bromsulphalein clearance reduced
 in fatty livers 86
 Bromsulphalein excretion in bile
 fistula dogs 86
 during cholestasis 86
 in heart failure 86
 Bromsulphalein extraction 139
 Bromsulphalein retention in con-
 gestive necrosis 208
 correction of 736
 Bromsulphalein retention test
 370-373
 evaluation of 373
 methods of 370-371
 technique in 371
 physiologic basis of 370
 results of 371
 in circulatory insufficiency
 372
 in experimental animals 372
 in hepatic cell damage
 371-372
 in nonhepatic disorders 372
 prolonged retention 372
 Brown atrophy 19 205
 hepatocellular iron in 20
 from undernutrition 503-504
 functional alterations in 503-504
 structural changes in 504
 Brucellosis 559 561-562
 differential diagnosis of 561
 hepatic disease from 561-562
 hepatic reaction in 561
 structural alterations in 561
 BSP (see Bromsulphalein)
 Bubonic plague 564
 Budd Chiari syndrome 481
 Burns 398
 Bush teils 400 518 519
 Butter yellow 398 593
 hepatic carcinoma from 507

C

- C bile 377
 C reactive protein 182 334
 Cadmium reaction 330
 Calcium 59
 in bile 81
 in gallbladder 116
 Calcium absorption 651
 Calcium salts 299
 Camphor 68 83
 Canalicular tuberculosis 558
 Canaliculi diverticula of 103
 Canicola fever 453
 Capacity tests 313
 Capillaria hepatica 572
 Capillary fragility 219 221
 Capillary permeability increased
 in ascites 295
 Capsular lymphatic vessels 150
 Capsule of Glisson 154
 Caput medusae 131 290

- Bile pigment excretion & influence of
 kidney on 650-651
- Bile pigment metabolism during
 blockade 101
 in cirrhosis 291
 in complete biliary obstruction
 183
 acholic stools in 183
 serum bilirubin in 138
 tumors in 183
 urobilinogen in 183
 in intrahepatic cholestasis 188-
 189
 in hepatocellular degeneration
 187
 in incomplete biliary obstruc-
 tion 183
 stones in 189
 structures in 189
 urobilinogen in 189
 in intrahepatic cholestasis 183
 199
 act of feces in 195
 tests based on 354-364
- Bile pigments 90
 abdominal retention of 185
 in bile 81
 enteropneumonia of 70
 78
 during hydrochloric acid 83
 nomenclature and chemistry of
 71-73
- Bile proteins 81
- Bile salts 81
 absorption of by gallbladder
 110
 administration of 293
 intravenous 84
- Bile secretion 165
 emotional factors in 83
 histologic changes during 84
- Bile stasis 225
- Bile syndrome insipidated 460
- Bil thrombi 183
- Bilharziasis (see Schistosomiasis)
- Biliary cirrhosis 28 469
 cholangitic 472
 congenital acholic 170
 infected 472
 secondary 472
- Biliary conductance and storage sys-
 tem enterobiliary intestinal
 by 113
- Biliary dyskinesia 298-299
- Biliary excretion of bilirubin 70-
 77
 of Bromsulphalein 372-373
 of elvesterol 36-37
- Biliary fistulas chemic 84
 internal 303-304
- Biliary function tests 314
- Biliary hepatitis 35 463-472
 chronic 472
 chronic infected 472
 structural changes in 472
 infected 471-472
 noninfected late results of 469
 purulent 471-472
- Biliary obstruction benign and
 malignant differential between
 666-667
 intrahepatic (see Extrahepatic
 biliary obstruction)
- Biliary obstruction intrahepatic
 184-185
 palliative surgery for 239
 prolonged green hue of skin in
 75
 serum cholesterol in 36
 termination of for long time 239
 urobilinogen in urine in 362
- Biliary pancreatitis 833
- Biliary passages carcinomas of
 613 616
- Biliary pressure 113
- Biliary shunt or sand 195
- Biliary stasis 299-301
- Biliary system function of 113-
 121
 lei of Achilles of 180
 malformations of 170-172
- Biliary tract benign epithelial tu-
 mors of 592
 non epithelial tumors of 610
 pain in 153-154
- Bil feces 75 78 199
- Bil grahns 376
- Bil rubin 27 70 72 75-76 81
 217 237 734
 in aqueous humor of eye 193
 in bile and feces 185
 determination of 359
 biliary excretion of 70-77
 in blood protein bound 76
 in body fluids 193
 in conjunctiva 199
 direct or prompt reacting (see
 prompt reacting below)
 formation of 75 199
 in cerebrospinal fluid 75
 indirect reacting 70
 and prompt reacting differ-
 ences between 76-77
 toxic effect of 673
 in mucous membranes 199
 ne types of 77
 in chilgriment 199
 in minute fraction 76
 precipitation of 299
 prompt reacting 70
 determination of 356-357
 results of 357
 technique of 356
 preceded in 357
 reactions for 36
 and indirect reacting differ-
 ences between 76-77
 ratio of to total bilirubin 181
 role of Kupffer cells in 77
 serum and tissue relation be-
 tween 193-199
 (See also Serum Bilirubin)
 skin 199
 in spinifid 193-199
 tests 199
 urinary excretion of 7-78
 in urine determination of 358
 359
 evaluation of 358-359
 methods of 358
 absorption tests 353
 foam test 358
 Gmelin Rosenbach test
 358
 methylene blue 358
 Smith test 358
- Bilirubin in urine determination
 of physiologic basis of
 358
 results of 358
 in acholic jaundice 358
 in hepatocellular degeneration
 187
 in viral hepatitis 78
 van den Bergh reaction of 76-
 77 354
 in vessels 199
 in Weiss disease 199
- Bilirubin degradation enteric 78
 following administration of
 antibiotics 78
 hepatic 78
 in gallbladder bile 78
- Bilirubin infarct of the newborn
 648
- Bilirubin partition 734
- Bilirubin stones in chronic he-
 molytic jaundice 300
 in sickle cell 300
 in thalassemia 300
- Bilirubin = tolerance test 356
- Bilirubinglobin 70
- Bilirubins two concept of e i
 dence against 77
- Bilirubinuria 237
 in hemolytic jaundice 77
- Bil erd n 72 199
- Bil erd n globin 75
- Bimucleated cells 83
 in regeneration 90
- Bio 379-395
 academic information obtained
 by changes in press e con-
 gest on 385
 changes in pregnancy 385
 chemical determinations of en-
 zymes fat vitamin A nu-
 cleic acid glycogen pro-
 tein 385
 cultures of biopsy tissue in tu-
 berculous 375
 histologic distribution of alkali
 phosphate 385
 histologic distribution of vi-
 tamin A 385
 adequacy of specimens in 383
 after are of patient in 381
 applications of 383-385
 aspiration 381
 causes of death in 382
 in children 384
 in cirrhosis 384
 contraindications to use of 382
 correlation of and biochemical
 findings 384-385
 cultures of 99
 dangers of 382-383
 diagnostic accuracy of 383
 in differential diagnosis of jaun-
 dice 384
 fatalities in 382
 gross inspection of specimen in
 381
 of hemangomas of liver 739
 in hepatitis 383-384
 indications for 381-382
 liver diagnostic superiority of
 over hepatic tests 281
 for metastatic tumors in liver 620

- Cholangogues 82
 Cholangiocarcinoma 599
 Cholangiofibrosis 597
 Cholangiographic studies intra
 venous 309
 Cholangiography direct 376
 intravenous 376-377
 operative 376
 oral 376-377
 percutaneous transhepatic 736
 peritoneoscopic 376
 Cholangiohepatoma 610
 Cholangioles 103
 Cholangiolitic hepatitis 424 738
 Cholangiolitis 185 193-195 197
 245-246 684
 acute 462
 allergic 403-404
 drug induced 737
 arsenical 403
 bacterial 198 245-246
 chronic 198 463-467 733
 clinical manifestations of
 463 465
 differential diagnosis of with
 xanthomas 467
 laboratory findings in 465
 structural alterations of 465
 treatment of 467
 xanthomatous form of 465-
 467
 and pericholangiolitis 462-467
 rapidly fatal 463
 subacute 462-463
 clinical manifestations of 462-
 463
 structural changes in 463
 Cholangioma 597
 Cholangiotoxic lesion 196
 Cholangitic abscess 235 246 584
 Cholangitis 184
 biliary pressure causing 113
 chronic obliterating 245 463
 cicatrizizing 246
 descending 246
 extrahepatic 248
 intrahepatic purulent 246-248
 causes of incompletely ob-
 structing lesions in com-
 mon or hepatic duct 246
 stones 246
 strictures 246
 tumors of papilla of Vater
 246
 clinical features of 248
 etiology of 246
 functional changes in 248
 pathogenesis of 246
 primary form of 246
 secondary form of 246
 structural changes in 246
 nonsuppurative 248
 purulent 84
 suppurative 248
 secondary to liver abscess 246
 Cholangitis lenta 245
 Cholate tolerance test, 366
 Cholates effect of on serum cho-
 lesterol 238
 Cholebilirubin 70
 Cholecystectomy colic after 298
 common duct after 309
 Cholecystectomy effect of on gall
 bladder and sphincter of Oddi
 119
 Cholecystitis 299 303-308
 acute 304-305
 bacteria in 304
 catarrhal 304
 chemical 304
 ulcerative or phlegmonous
 304
 vascular 304-305
 acute gaseous 304
 in children causing hydrops of
 gallbladder 308
 chronic 305-306
 calculated 306
 calculous 306
 cholesterolosis 306
 chronic chemical 306
 contracted gallbladder 306
 cystic duct obstruction in 306
 empyema 306
 diagnosis of 307-308
 glandular proliferating 306
 incidence of 307
 pathogenesis of bacteria in 307
 chemical irritation 307
 stasis in 307
 recurrent 306
 sequelae of erosion of cystic ar-
 tery with hemorrhage 308
 internal biliary fistulas 308
 perforation with bile periton-
 itis 308
 percholecystic and subphrenic
 abscesses 308
 percholecystitis 308
 Cholecystitis glandularis prolif-
 ans 592
 Cholecystography 374-376
 evaluation of 376
 methods of 374
 physiologic basis of 374
 results of 375-376
 contrast visualization 375
 motility 375
 nonvisualization 375-376
 causes of 375-376
 variations in size shape and
 contour 375
 Cholecystokinin 117 298
 Cholelithiasis 299-304
 in chronic liver disease 300
 laboratory diagnosis of 304
 and pregnancy 301
 Cholema 219
 Choleme simple familiale 186
 Cholesteres 82
 bile salts as 66
 Cholestasis 189-196 225-239
 changes in other organs in focal
 mechanical obstruction
 237
 by abscesses 237
 by aneurysm of hepatic ar-
 tery 237
 by parasites 237
 by tumors 237
 chronic intrahepatic 238
 clinical manifestations of and
 revia 239
 bleeding 239
 excoriations 239
 malaise 239
 severe itching 239
 extrahepatic (see Extrahepatic
 cholestasis)
 features of common to all
 forms 225-229
 bile stasis and extravasation
 225
 hepatic cell degeneration
 225 227
 hepatic cell necrosis 227-
 228
 inflammation 229
 proliferation of ductules and
 ducts 228-229
 functional consequences of 237-
 239
 hepatocellular degeneration
 238
 inflammation 238
 regurgitation of biliary con-
 stituents 237
 elevation of serum phospho-
 lipid levels in 237
 hemorrhagic tendencies in
 237
 histamine content of blood
 in 237
 specific alterations of hepatic
 function 238-239
 alkaline phosphatase 239
 cholesterol 238-239
 depression factor 239
 phospholipids 238
 intrahepatic (see Intrahepatic
 cholestasis)
 local 193
 morphologic appearance of 225-
 237
 primary drug induced 737
 prolonged producing periductu-
 lar fibrosis 235
 prolonged extrahepatic feathery
 degeneration in 203
 prolonged intrahepatic feathery
 degeneration in 203
 serum alkaline phosphatase in
 341
 simple 463
 symptomatic relief of adenosine
 monophosphate for 239
 antihistamines for 239
 cortisone for 239
 intravenous procaine for 239
 methyltestosterone for 239
 total serum cholesterol in 350-
 351
 types of cirrhosis related to 472

- Carbarsone 737
 Carbohydrate intake excess 496
 Carbohydrate intermediates tests concerning lactic acid tolerance test 347
 serum citrate 347
 serum lactate 347
 serum pyruvate 347
 Carbohydrate metabolism 30-32
 215
 effect of insulin on 639
 and mitochondria 21
 tests based on 344-347
 bilod glucose 344
 galactose tolerance test (see Galactose tolerance test)
 glucose tolerance test 344
 levulose tolerance test 344-345
 Carbohydrate stains 11
 Carbohydrates 25
 protein bound 733
 relation of to metabolic pool 25
 Carbon tetrachloride 393-400
 593 733
 Carbon tetrachloride intoxication 46
 acute 394
 chronic 394
 and hepatic lymph 151
 Carbonates in bile 81
 Carbonic anhydrase inhibitors precipitating hepatic coma 735
 Carcinogenesis experimental 593-599
 factors in 593-595
 accelerating factors 595
 age sex and genetic factors 595
 chemical carcinogens 593
 inhibiting factors 595
 nutritional factors 593
 tumor inducing factors 595
 Carcinogens effect on vitamin A 53
 Carcinoma of biliary duct arising at bifurcation of common hepatic duct 189
 of duodenum 189
 of gallbladder 189
 of head of pancreas 189
 of papilla of Vater 189
 of biliary passages 613-616
 differentiation of cirrhosis from 666
 of ducts 304
 ductular origin of 599
 of extrahepatic bile ducts 614-615
 clinical manifestations of 614
 etiology of 614
 incidence of 614
 laboratory findings in 614-615
 structural alterations in 615
 therapy for 615
 format of differentiation of bile on 304
 in hemochromatosis 536
 pathways of 600-601
 site of 599-600
 Carcinoma of gallbladder 304
 615-616
 clinical manifestations of 616
 etiology of 615
 incidence of 615-616
 structural alterations in 616
 gastrointestinal 632
 hepatic from butter yellow 597
 Iepatocellular vs cholangio cellular 599
 and cirrhosis frequent coincidence of 28
 in neurotic liver 263
 of intrahepatic bile ducts 613-614
 clinical manifestations of 613
 structural alterations in 614
 metastatic in cirrhotic liver 252
 of pancreas 633
 primary vs cirrhosis 666
 vs secondary 612
 primary hepatic (see Primary hepatic carcinoma)
 proved detection of metastases in 619
 regenerative nodules 612
 secondary vs cirrhosis 666
 in typical malnutrition 518
 uterine 644
 Carcinosis 610
 Cardiac cirrhosis 480
 Cardiac output 219
 in cirrhosis 651
 in liver disease 651
 in severe hepatic failure 651
 in viral hepatitis 651
 Cardiovascular system effect of liver on 651
 and liver relation between 651
 Carotid solution 10
 Carotene 5-
 in liver 55
 transport of to liver 52
 Carotenemia 199
 Carotenois 5-
 Carotene react on for determination of plasma vitamin A 366
 Castrol on 645
 Citric acid 573
 Catabolism nucleoprotein 45
 of proteins 44-45
 Catalase 16 50
 Catheter 16
 Cavernomatous transformation 141
 Celiac axis 122
 Cell division 87
 Cell of ganelli 20-21
 Celluloid 10
 Cells biocultured 88 90
 Central nervous system and liver relation between 652-653
 manifestations of 219
 Cephalin 25 33
 Cephalin cholesterol-flocculation test 326-325
 valuation of 327-328
 method of 326
 physiological basis of 3-6
 preparation of emulsions for 3-6
 procedure in 3-6
 reagents for 326
 Cephalin-cholesterol-flocculation test results of 326-327
 in cholestasis 327
 in chronic passive congestion 327
 in cirrhosis 327
 in hepatic tumor metastases 327
 in hepatitis 326
 in infectious mononucleosis 327
 in malaria 327
 in rheumatoid arthritis 327
 in tuberculosis 327
 technique of 326
 Cephalin flocculation in animal 668-669
 Cephalin flocculation test 239
 Ceroid 11 19 493-499
 Ceruloplasmin 61 541
 Cistodes 575
 Charcot fever 245 471
 Chemical analysis 12-13
 of desoxyribose nucleic acid (DNA) 13
 of glycogen 12
 reference point of 13
 of water content 12
 Chemical changes in liver in hepatic cell degeneration 213-214
 electrolytes 214
 enzymes 213-214
 glycogen disappearance 213
 increased water content 213
 lipids 213
 nitrogenous substances 213
 in serum and urine in hepatic cell degeneration 215-219
 in severe hepatic failure 218-219
 in hepatectomized animals 218
 in humans 218-219
 lipids 219
 minerals 219
 nitrogenous substances 218-219
 in urine 217-218
 Chemical irritation in cholecystitis 307
 Chemistry of bile acids 63-64
 Chans disease clinical and laboratory finding in 431
 etiology of 481
 structural changes in 481
 Chans syndrome 145 234
 Chinese liver fluke 572
 Chloranilic acid test 331
 Chloride 59-59
 in bile 81
 content of in liver 58
 in cytoplasm 12
 determination of 367
 in hepatic disorders 59
 Chlorinated naphthalene 396 400
 Chloroform 394 401
 Chlorpromazine 196 2 9
 Chlorpromazine induced cholangitis 737
 Chlorpromazine jaundice 404 737
 Chlorotetracycline 402
 Chologogic agents 119

- Cirrhosis posthepatic** 449
 postnecrotic 263-266 278 446
 449-451 735
 in animals 266
 clinical features of 450
 histologic alterations of 450-451
 biopsy specimens 451 452
 necropsy specimens 450-451
 of Karsner 266
 laboratory findings in 450
 macroscopic appearance of 450
 pathogenesis of 451
 processes damaging intact parenchyma angulation of vessels 263
 approximation of portal and central fields 263
 fissures 263
 nodular regeneration 263
 nodules 263
 portal inflammation 263
primary biliary (*see* Cholangiolitis chronic)
primary carcinoma vs 666
 processes common to all types of 272-278
progressive alcoholic (*see* Florid cirrhosis)
 proposed nomenclature of 531
 race distribution in 521
 recognition of without jaundice 531
 relation of human primary hepatic carcinoma to 662-663
 relation of structural and functional alterations in 280-283
 fatty metamorphosis 281
 hepatocellular degeneration 280-281
 bile pigment metabolism 281
 endocrine changes 281
 lipids 281
 serum protein alterations 281
 inflammation 282
 regeneration 281-282
 scarring 282-283
renal function in 650
 resulting from obstruction 235
 secondary biliary 171 235 738
 secondary carcinoma vs 666
 secondary collapse in 266
septal (*see* Septum formation primary)
 as sequela to fatty metamorphosis 254
 serum alkaline phosphatase in 341
 sex distribution in 21 522
 splenomegaly 287 623
 from spotty necrotic hepatitis 446
 structural changes in 520
 structural criteria for 524
 structural features of 262-279
 subacute portal (*see* Florid cirrhosis)
 symptoms in 522
- Cirrhosis toxic** 449
 of Mallory 266
 transition of fatty liver into 510
 and tuberculosis 552 555
 types of related to cholestasis 472
 in thyrotoxicosis 485
 types of septums transforming fatty liver into 270
 in ulcerative colitis 631
 urobilinogen in urine in 361
 and Wernicke's hemorrhagic po-
 hocephalitis 56
 xanthomatous biliary 196 238 463
Cirrhotic mothers children born of 520
Cirrhotic process arrest of criteria for 530
 extent of 5-6 528
 clinical criteria for 526
 laboratory criteria for 526 5-8
 structural criteria for 528
 rate of progression of 528-530
 clinical criteria for 528
 laboratory criteria for 528
 structural criteria for 528 530
Cirrhotic transformation 411
Citrate 25
Citrate intoxication 215
Citrulline 27
Clasmatocytes 99
Clonorchis sinensis 193 572
Clonus 223
Cloudy swelling 202
Cobalt 62
 in bile 81
Coccarboxylase 56
Cocciidiomycosis 567
Coccidium cucullis 572
Coenzyme A 26 28
Coenzymes I and II 57
Colchicine 83 396
Colitis (*see* Ulcerative colitis)
 Collagen content of liver 93
 Collagenization of preformed fibers 255
Collagenosis 259
Collapse 263-266 447
 central from chronic passive congestion 256
 from repeated exposures to bromobenzene 256
 from repeated exposures to carbon tetrachloride 256
 of entire lobules following massive necrosis 256
 fibrosis following 256-259
 focal intralobular 259
 perportal 256 259
 secondary 272
 in cirrhosis 266
 submassive following repeated episodes of focal necrosis 256
 by prolonged ethionine feeding 256
 in protracted human viral hepatitis 256
Collateral circulation 289-290
Collaterals additional creation of 291
- Collaterals extrahepatic development of in animals** 141
Colloid osmotic pressure 294
Colloidal gold 396
Colloidal gold-flocculation test 330-331
Colloidal iron in phagocytosis 98
Colloidal red test 331
Colloids injected in Kupffer cells 101
Coma hepatic 219 221-224 735
 administration of glutamic acid in 223
 administration of nitrogenous substance in severe liver disease precipitating 223
 anatomic changes in 222
 clinical manifestations of 221-222
 cholemic crying 222
 clasp knife rigidity 222
 delta wave activity 222
 duration of precomatose and comatose states 222
 electroencephalographic changes 222
 flapping tremor 222
 impending coma 222
 pyramidal signs 222
 mechanism of 222-223
 ammonia or ammonialike substances 223
 breakdown products of liver tissue 222
 disturbance of intermediary metabolism of carbohydrates 222
 drop in level of plasma cholinesterase with rise in acetylcholine 222
 failure of detoxification 223
 hypoglycemia 222
 presence of excess amino acids 223
 specific supporting influence upon brain metabolism 223
 precipitating factors in associated malnutrition 224
 bilirubinities 224
 excess fluid administration 224
 excess nitrogen absorption from blood in gastrointestinal tract 224
 hemorrhage from esophageal varices 224
 injudicious use of sedatives 224
 opiates 224
 respiratory alkalosis in 735
Common bile duct after cholecystectomy 309
 incomplete obstruction of 303
 intermittent complete obstruction of 303
 length of 106
 ligation of 35
 increasing hepatic lymph 151
 obstruction of 303
 termination of 109-110 632
Complement titer 334

- (1) sterol 28 34-37 237 307
 absorption of, 35
 bv gallbladder 116
 amount of 35
 antihypertensive effect of 36
 in arterial hepatic injury 233
 in bile 81
 bile acids from 36-37
 biliary excretion of 36-37
 breakdown of 36
 in chronic intrahepatic cholestasis 238
 degradation of 35
 enterohepatic circulation of 37
 excess dietary 35
 in experimental hepatic injury 238
 in extrahepatic biliary obstruction, 235
 in fatty livers 35
 formation of 35
 duri hydrocholeric 83
 in infectious hepatitis 238
 large amounts of feeding of 496
 and phospholipid relation between 36
 precipitation of 299
 protein binding of 36
 role of Kupfer cells in 100
 serum (see Serum cholesterol)
 sources of 35
 synthesis of rate of 35
 sites of 35
 transformation of 68
 type of 35
 in xanthomatous biliary cirrhosis 238
 Cholesterol ester percentage 219
 Cholesterol/ester ratio 238
 in cirrhosis 231
 Cholesterol esterase 36 49
 Cholesterol esterification 352
 Cholesterol esters 25 35
 in serum cholesterol 351-352
 Cholesterol feeding reduced phospholipid turnover after 36
 Cholesterol intake excessive 35
 Cholesterol level 219
 Cholesterol storage disease 545
 Cholesterol 35 306
 Cholesterol 63 67 81
 conjugation of 74
 Choline 25 27 34 37 252
 administration of 500-501
 in cirrhosis 514
 in fatty livers 39
 for cholesterol fatty liver 36
 effect of on phospholipid turnover 34
 in intoxications 38
 Choline content of fatty liver 39
 Choline deficiency 34
 nutritional human 39
 prolonged 37
 relief 496
 Choline deficient diet 37
 and thiamine 57
 Choline deficient fatty liver 37
 Choline oxide 34 37
 Choline requirement 37
 Choline tera 342
 after bombazone treatment 49
 Cholinesterase after butyrylcholinesterase
 intoxications 49
 after carbon tetrachloride intoxication 49
 in malnourished infants 49
 red cell 49
 Cholestase level 238
 Cholografin 3-6 647
 Cholelithiasis 84
 Chromatin 21
 deoxyribonucleic acids of 87
 nuclear 16
 nucleolus associated 22
 residual 21
 Chromium radioactive in phagocytosis 98
 Chromium intoxication 401
 Clostridium 305 644
 Cinchophen 67 82 83 402
 effect of on hepatic arterial blood flow 143
 Cinchophen-oxidation test 370
 Cinnamic acid 67 69
 Cinnamic acid test 369
 Cinnamyl glucuronates 68
 Circulation at birth 167
 collateral 259-290
 enterohepatic (see Enterohepatic circulation)
 fetal 167 168
 (See also Hepatic circulation)
 Circulation time 651
 portal 140
 Circulatory changes effect of on liver 651
 Circulatory embarrassment as sequelae of ascites 295
 Cirrhosis and acute hepatitis differential diagnosis between 668
 age distribution in 520 522
 alcoholic 63
 arterial hypertension in 651
 as cause of diabetes 523
 basal functional alterations in effect upon hepatocellular structure and function 280
 portal hypertension 280
 systemic effects 250
 biliary (see Biliary cirrhosis)
 in biopsy specimens 529 530
 as cause of intrahepatic cholestasis 196
 in children 50 738
 cholelithiasis (see Cholangiolithiasis chronic)
 cholelithiasis 235 245 472
 cholelithiasis 469
 classification of 278-279
 clinical evaluation of criteria for 523
 clinical manifestations of 50 522-523
 clinical problems and classification of 50-531
 consequence of alkalimetric 266
 in congenital 449
 congenital 424
 congestive or cardiac 480
 definition of 26
 derivation of term 26
 descriptive classification of 278
- Carcinoma differential diagnosis of by laboratory tests 531
 differential of from carcinoma 666
 diffuse septal 565
 etiologic classification of 279 523-524
 etiologic types of recognition of 523
 etiology and morphology of relation between 524
 evaluation of criteria for 525
 fibrovascular 545
 finger nail changes in 523
 focal (see Focal cirrhosis)
 formation of 398
 functional changes in 280-297
 functional classification of 279
 functional therapeutic classification of 524-530
 of Hannon 196 272
 hemorrhagic ascitic fluid in 221
 hepatic blood flow in 138 282
 hepatic tests in poor correlation between histologic findings and results of 281
 and hepatocellular carcinoma frequent coincidence of 282
 hepatocellular damage in degree of 525-526
 clinical criteria for 525
 jaundice in cirrhosis 526
 laboratory criteria for 526
 structural criteria for 526
 human 526
 hypertrophic of Hannon 463
 incidence of in autopsies 520
 infected obstructive 472
 with jaundice 526
 laboratory criteria for 524
 Laennec's (see Laennec's cirrhosis)
 latent, 291 528
 liver biopsy in 334
 malnourished 459
 Marchand 266
 metastatic carcinoma in 282
 morphogenetic classification of 278-279 523
 morphogenesis of 278-279
 morphology of 266
 multiplicity in 523
 multifocal of Sabouni 266
 nomenclature of 266
 nutritional (see Nutritional cirrhosis)
 obstructive 469
 and peptic ulcer coexistence of 63
 pericholangitic biliary 196 463
 physical findings in 522-523
 pigmented 535
 pneumonia in schistosomiasis 575
 pneumonia cholangitic 245
 and polynucleus 56
 in polyphagia 79
 portal 279
 portal hypertension in 284
 in steatosis (see postnecrotic below)

- Diabetes mellitus hepatic structure
in changes in histo-
logic findings in 642
glycogen in nuclei 642
macroscopic appearance in
642
hepatogenic 344
and liver 640-643
and nuclear glycogen 22
Diabetogenesis alloxan 640
Diaphragmatic veins of Retzius
133
Diarrhea in infants 632
Diaz reaction of van den Bergh
70
total serum bilirubin based on
355-356
Diaz reagent 76
Dicrocoelium dendriticum 573
Dicumarol 221
Diet in acute viral hepatitis 426
choline deficient 37 57
high carbohydrate 500
high fat 500
high protein 500
as therapy for ascites 296-297
influencing results of tests 662
low fat and low carbohydrate
496
low protein 493 500
necrogenic 499
protein deficient 23 46
threonine deficient 38
Dietary imbalance 496-501
Dietary necrosis 499-500
etiologic factors in 499
functional changes in 499
metabolic lesion in 738
pathogenesis of 499-500
structural alterations in 499
acute necrosis 499
chronic changes 499
Diethylstilbestrol 399
Digitoxin 147
Dihydrobilirubin 78
Dilantin 402
Dilatation of abdominal veins in
portal hypertension 290
of junctional veins 290
of veins in all layers of esopha-
gus in portal hypertension
290
extending into cardiac end of
stomach 290
Dilated veins rupture of in peptic
digestion of mucosa 290
Dilation turbidity test 330
for kala azar 330
Dimethylaminobenzene 593
Dinitrobenzene 401
Dinitrophenol 401
Diodrast 377
Diphtheria toxin 396
Dipyrroles 73 75
Disse spaces of (see Spaces of
Disse)
Diurnal rhythm relation of to
glycogen 84
of renal function 296
Diverticula of canaliculi 103
of gallbladder 112
DNA (see Desoxyribose nucleic
acid)
- Dog liver anaerobic bacteria in
99
Drugs antituberculous 402
in bile 81
cholekinetic effect on gallblad-
der and sphincter of Oddi
119
Dry freezing of hepatic phospho-
tase 47
Dry freezing techniques 10
Dubin Johnson syndrome 187 735
Duct of Santorini 632
of Wirsung 632
Ductal systems biliary and pan-
creatic reflux between 119
Ducts aberrant 106 171
accessory 106 112
carcinomas of 304
inflamed spontaneous rupture
of 248
intrinsic muscles of 109
proliferation of 228-229
in parabiotic partners of rats
with ligated common ducts
229
in rats with ligated hepatic
ducts 229
Ductular permeability altered 195
Ductular proliferations 119-120
cysts of 120
Ductules 90
intralobular 106
obstruction of 184
perilobular 106
proliferated organ of 120
proliferation of 228-229
serum alkaline phosphatase in
48
Ductus venosus Arantii 167
Duodenal contents application of
methods of extractive citol-
ogy to 378
Duodenal drainage 304 308 377-
378
chemical examination in 378
evaluation of 378
inspection of bile in 378
microbiologic examination in
378
microscopic examination in 378
procedure for 377-378
Dye Azorubin S 85 86 647
Bromsulphalein (see Broms 1
phalein)
fluorescein 85 199
phenolphthalein 86
rose bengal 85 86
storage of in liver 86
trypan blue 85 102 396
Dye excretion 85-86
competition for 85
dynamics of 85-86
chemical nature of dye 85
circulatory influences 86
metabolic influences 85-86
role of hepatic function 86
role of kidney 85
histology of 85
Dye-excretion tests 370-373
Dyskinesia 298 303
atomic 298 299
biliary 298-299
- Dyskinesia contraction of gallblad-
der incoordination relax-
ation of sphincter of Oddi
298
hyperkinetic 298-299
causes of 299
sequelae of 299
pain reaction in 298
Dyspepsia and neurasthenia 440-
441
Dyssynergia 298
- ## E
- Echinococcus cyst (see Hydatid
disease)
Eck fistula 142 218 223 277 291
and dye excretion 86
in regeneration 93
reversed 142
Eck fistula dogs 42 82
cholesterol in 35
Eclampsia hepatic necrosis in
485-488
clinical manifestations of he-
patic changes in 486
Laboratory findings in 486
pathogenesis of 485-486
structural alterations in 486
488
histologic changes 486
macroscopic appearance
486
other hepatic changes in
pregnancy 486 488
Edema 240-241
bilirubin in 193
etiologic factors in 240
functional significance of 241
hepatic produced by histamine
in dogs 241
produced by urethane and
allil formate in rats 241
intestinal 630
malnutrition as cause of 240
of portal tracts 235
pulmonary 221
resulting in congestion 240
structural changes in 240-241
toxic 241
Edema formation as sequela of
ascites 295-296
Stirling's law of 293
Ehrlich's aldehyde reaction 73
Ehrlich's aldehyde reagent 70 79
for determination of urobilin-
ogen in urine 359 360
Elastin 199
Electrocardiogram in liver disease
in cirrhosis 651
in severe hepatic failure 651
in viral hepatitis 651
Electrocardiographic changes and
myocarditis 737
Electrolytes absorption of by gall-
bladder 116
tests concerning 366-367
Electroplasma 42 316-318
paper 316-317 733
zone 316
Electroplasma protein patterns
317-318
Elms 14 120

- Concave disease 451
 Conditioned deficiency 69 214
 Congestive acute passive of liver 474-4 8
 chronic passive of liver 474 478
 1) pyogenic in 4 7
 clinical and laboratory findings in 477
 histologic changes in 477-478
 central collipsis and fibrosis 478
 central necrosis 477 4 9
 jaundice in heart failure 474 477
 macroscopic appearance of 477
 effect of on liver 473-474
 hepatic in thyrotoxicosis 483-485
 human hepatic injury from 474-481
 passive of liver 474
 Congestive cirrhosis 480
 Congestive fibrosis of liver 4 8 480
 functional significance of 478
 structural alterations in 475 480
 histologic changes 480
 macroscopic appearance 478 480
 Congestive hepatic injury 473-481
 experimental studies in 473-4 4
 jaundice in 733
 Cong red 102
 Conjugation 67-68
 Connective tissue increase of (see Fibrosis)
 Connective tissue stains 10 11
 Constitutional hepatic dysfunction 187
 Contrast visual ratio 774
 Conversion (see Factor II)
 Cooney but 298
 Copper 61-62
 n bile 81
 excretion of in urine 541
 Copper metabolism disturbance of 541
 Copper porphyrin 72 73 364
 Coproporphyrin I in bile 79
 n jaundice 79
 n urine 79
 Coproporphyrin III 74 79
 n alcohol in 79
 Cysteine 25 30
 Constrictor 30
 Cystic 20
 Corpus luteum hormones influence of 645
 Corset 170
 Costochondral and regeneration 93
 urinary excretion of in liver disease 638-639
 Corticotropin (see ACTH)
 Cortison 32 44
 n acute viral hepatitis 418
 in animals 637
 effect of on phospholipid metabolism 34
 Cortison in man 637-638
 1) acute hepatitis 637
 in cirrhosis 637
 in hepatic diseases 637
 in non-hepatic diseases 637
 Cushingoid bodies 415 430 450
 Cytoceres law 468
 Cytidine 27 38
 formation of 45
 Cytosine 27 35 217 218
 in bile 81
 Crude oil on regenerative potentialities of liver 83
 Crude oil Bismarck disease 133
 part of Bismarck disease 298
 Crude oil Bismarck syndrome 298
 Crude oil disease 481
 Cytoceres porphyria 79
 Cyanic acid 477
 Cyclic phosphate system 25
 Cylindric 183
 Cystic 392
 Cystic 27 87
 Cystic duct 105 112
 calculous obstruction of 303
 function of in gallbladder 115
 histologic value of 112
 neonatal obstruction of 303
 variations of 112
 Cystic duct obstruction 303
 in chronic cholecystitis 303
 Cystic duct of Calot 112 112
 Cystic duct 25 34 38 218
 urinary excretion of 45
 Cystine deficiency 490
 Cystic ligaments 173
 Cysts 10
 1) cholecystitis 171-172
 infection of cyst wall in 12
 clinical features of 171
 diagnosis in 172
 Malignant and carcinomas in 172
 histology 249 251
 histology 490-530
 clinical manifestations of 530-550
 differential diagnosis of 530
 structural alterations in 530
 Cytoceres albanicus 12
 Cytochrome 21
 cell of 202
 Cytoceres enzymes 25
 Cytochrome oxidase 48 50
 in mitochondria 22
 Cytologic demonstration of alkalinic phosphatase 47
 Cytologic excretion application of methods of to duodenal contents 378
 Cytochrome oxidase in hepatitis 456
 Cytoplasm 14
 of bile in Kupffer cells 227
 in liver cells 12
 pentose nucleosides of 16 18
 protein depletion in 15
 protein toxicity in 15
 proteins of 25-18
 histology 15
 Cytoplasmic proteins of labile 15
 nuclear 10
 stannin in 15
 (See also Liver cell cytoplasm)
 Cytoplasmic histophagia of Kupffer cell and increased serum gamma globulin level correlation between 100
 Cytotoxic coagulation 202-203 735
 Cytotoxic granules 18-20
 Cytotoxic protein synthesis 23
 Cytotoxicity 19 20
 Cytotoxicity 534
 Cytosine 18
 D
 D-amino acidase in mitochondria 21
 d-urobilin 78 734
 d-urobilinogen 73 734
 in bile 78
 D-lactate 30
 Dark adaptation in cirrhosis 33
 DPK 400 401 593
 Deamination 26-27 44
 D-gradation of alkaloids 87
 1) D-graminol 87
 of digitals 87
 of ergot alkaloids 87
 of opiates 87
 of quinine 87
 of steroid hormones 87
 D-lydrolysis 72
 D-lydrochol acids 83
 Dihydroxybenzylrubin 72
 D-glucosylase 50
 D-oxon factor 323
 Dehydration of fatty acids 32
 D-sucrotyl coenzyme 635
 and regeneration 93
 D-oxypentose nucleic acids (DNA) 21 18 21 92
 of chromatin 87
 constitutive of 21
 and Feulgen reaction 21
 and methyl green reaction 21
 D-oxypentose nucleic acids content of cells 21
 Desoxyribonuclease in mitochondria 21
 Detergents in phagocytosis 93
 Detoxification 50 67
 of benzene 68
 concentration of 67-69
 lack of in hepatectomized dog 68
 (See also Transformations)
 Deuteromorphin 79
 Diabetes mellitus 29
 clinical 640-641
 experimental 640
 galactos 543
 hepatic dysfunction in 641-642
 hepatic glycogen in 640-641
 hepatic structure in changes in 642-643
 fatty liver-cirrhosis syndrome in 642
 gallbladder disease in 643
 hepatitis in 643

- Fasciola hepatica* 193 572-573
739
- Fat appearing and disappearing 252
- central necrosis without 396
- centrolobular in alcoholic persons, 251
- in choline deficiency 251
- diffuse 251-252
- distribution of in cell 18
- in hepatic cell 249 251
- diffuse small droplet pattern of 249
- fatty cysts 249
- large droplet deposition of 249
- perinuclear or peribiliary pattern of 249
- perisinusoidal pattern of 249
- fecal 84 35-353
- histologic relation of to chemical fat 252
- intermediary in carbon tetrachloride intoxication 251
- in passive congestion 251
- in toxic central necrosis 251
- intolerance for 219
- for intravenous injection 100
- Kupffer cell 251
- lobular distribution of 251-252
- neutral (see Neutral fat)
- patchy distribution of 252
- peripheral after administration of anterior pituitary preparations to starving rats 251
- in malnutrition 251
- in nutritional fatty livers 251
- in protein deficiency 251
- in portal tracts 251
- and regeneration 93
- scattered 251
- in extremely high carbohydrate diet 251
- storage 28
- in thoracic duct lymph 33
- Fat absorption 33
- bile in 734
- Fat content of Kupffer cell 100
- Fat deposition hepatic effect of sex hormones on 645-646
- Fat intake excess 496
- Fat intolerance in gallbladder 309
- Fat metabolism 100 215
- effect of insulin on 639
- tests based on 347-353
- cholesterol esterification 352
- fecal fat 352-353
- lipid tolerance tests 353
- ratios of serum lipid fractions 354
- serum cholesterol (see Serum cholesterol determination of)
- serum neutral fat 348
- serum phospholipid 348-349
- total serum lipids 347-348
- Fat plancerosis 252
- Fat stains 11
- Fat storage in Kupffer cells 100
- Fat transport 32
- Fatty acid dehydrogenase 32
- Fatty acid oxidation 25
- Fatty acid synthesis 26
- Fatty acids 25 32
- arachidonic 32
- in bile 81
- desaturation of 32
- emulsifying effects of 299
- linoleic 32
- linolenic 32
- long chain 25
- saturated 25 32
- storage of 32
- unsaturated 25 32 34
- uptake of 32
- Fatty cysts 249
- in rats or mice on choline deficient diets 249 251
- Fatty degeneration 252
- Fatty liver 28 39 635
- in alcoholic persons (see Alcoholic persons fatty liver in)
- by carbon tetrachloride 253
- choline content of 39
- choline deficient 37 252
- by choline deficient diet 253
- coenzyme A content of liver in 738
- effect of threonine on 57
- by ethionine administration 253
- experimental observations of 253-254
- fatty acids in 32
- functional integrity of 735
- functional manifestations of 253-254
- in gargolism 253
- with hepatic failure 196
- by high fat-low protein diet 253
- in mongolism 253
- without necrosis 398
- nutritional (see Nutritional fatty liver)
- in obesity 503
- of pancrectomized dogs 38
- portal hypertension in 284
- rapid transition of into cirrhosis (see Florid cirrhosis)
- in rats fed human diets 738
- relation of to pantothenic acid deficiency 57
- in threonine deficiency 38
- transition of into cirrhosis 510
- Fatty liver-cirrhosis syndrome in diabetes 642
- experimental 496-499
- from malnutrition 504-519
- nutritional complicating factors in role of 504-505
- Fatty metamorphosis 249-254
- basic factors of 252-253
- central necrosis with 393-396
- in cirrhosis 281
- diffuse 251
- etiologic factors of examples of 253
- etiology of 252-253
- mechanisms of 253
- interplay of 253
- morphology of 249-252
- nutritional cirrhosis with (see Nutritional cirrhosis with fatty metamorphosis)
- observations of in man 254
- portal 738
- Fatty metamorphosis portal hypertension caused by 284
- of proximal convoluted tubules 648
- septum formation in 269-270
- sequelae of acute necrosis 254
- cirrhosis 254
- fibrosis 254
- hepatoma formation 254
- sudden death 254
- in tuberculosis 555
- Fatthry degeneration 203 205 227 232
- necrosis following 227
- in prolonged intrahepatic or extrahepatic cholestasis 203
- Fecal fat 352-353
- and bile 84
- Fecal urobilinogen 185 237
- determination of 363-364
- evaluation of 364
- methods of Schlesinger test 363
- Schmidt test 363
- physiologic basis of 363
- results of 363-364
- Ferritin 19 44 59-61 733
- Fetal circulation 167 168
- Fetal development later at largest relative size 167
- lobes 167
- lobules 167
- Fetal hemoglobin 186
- Fetor hepaticus 221 735
- Feulgen reaction 11
- Fibers 255
- intralobular formation of 259
- performed changes of 255-256
- Fibrin thrombi 485
- Fibrinogen 41 43 216 219 281 316
- in cirrhosis 43
- in fatal hepatic insufficiency 43
- after hepatectomy 43
- Fibrinogen levels high 317
- Fibrinogenopenia 43
- Fibroadenoma 289
- Fibrogenic splenomegaly 287
- Fibrocystic disease of pancreas postnecrotic cirrhosis in 739
- Filomas 616
- Filosis 616
- Fibrosis 255-261
- biliary 469 471
- chemical measurement and regression of by butter yellow intoxication 261
- by chronic carbon tetrachloride intoxication 281
- without cirrhosis little functional significance of 255
- following collapse 256-259
- congestive of liver 478 480
- cystic 633
- development of in hepatic tubercle 555
- forms of 255-261
- in fatal disease of the new born 489 491
- of liver associated with portal hypertension 739
- from new formation of fibers or membranes 259-261

- Embolism amniotic fluid 241
 of aorta 145
 retrograde 583
 Embryology of liver 163-169
 species differences in mammals
 vores 169
 in herbivores 169
 in omnivores 169
 Embryonal development and regeneration similarities between 168
 Emetine 402
 Emotional factors in secretion of bile 83
 Empyema 301 308
 Encephalitis in acute viral hepatitis 737
 Encephalopathy ammoniacal 224
 portosystemic 223
Endamoeba histolytica 569
 Endocarditis subacute bacterial 99
 Endocrine changes in cirrhosis 281
 Endocrine glands relation of liver to 635-648
 Endothelial cells vs Kupffer cells 96
 Endothelial damage 398
 Energy provision in metabolic function 25-27
 Enteritis 632
 amebic hepatomegaly due to 359
 Enterohepatic circulation 64-65
 of bile pigments 70 78
 of cholesterol 37
 Enzymes 46-51 217
 in bile 81
 branching 30
 debranching 30
 effect of irradiation on 656-657
 in liver tissue 48
 in mitochondria 21
 proteolytic 28 50
 reducing bilirubin to bilirubin 76
 in regenerating liver 92
 in serum tissue 46
 tests based on 340-344
 serum alkaline phosphatase 340-342
 serum amylase 343-344
 serum esterase 342-343
 Eosinophilic degeneration 20
 Eosinophilic infiltrations 559
 Eosinophilic nuclear inclusions 11
 regeneration 90
 Eosinophilic phagocytosis of 99
 Epinephrine 147 635
 effect of on hepatic glucose output 146
 on splanchnic oxygen consumption 146
 creasing portal pressure 296
 and portal pressure 59
 Eppinger's theory of jaundice 179-180 182
 Erythema nodosum 559
 Erythroblastosis fetalis 488 624
 Erythrocyte 98
 life span of in cirrhosis 628
 Erythrocyte sedimentation rate 333-334
 Erythrocytic nuclear maturation principle 57
 Erythrophagocytosis in hemolytic miasis 99
 in hemolytic anemia 99
 in sickle-cell anemia 99
 Erythropoiesis excessive in hemolytic disease of the newborn 489
 Esenb 147
 Esophageal varices in amebic hepatitis 290
 association of with spider nevi 290
 in carcinoma of liver 290
 in cirrhosis 290
 hemorrhage from 133
 obliteration of by injection of sclerosing fluids 290
 in portal hypertension 284 290
 in pregnancy 290
 in viral hepatitis 290
 Esophagogastric anastomosis 292
 Esterase activity 12
 reduced 49
 relation of to hepatocellular necrosis 49
 and simple fatty metamorphosis 49
 Esterase level 235
 Esterases 49 213
 biochemical demonstration of 46 49
 (See also Serum esterase)
 Estradiol 67
 Estrogen administration 645
 Estrogen inactivating function of liver 737
 Estrogen inactivation metabolism 643-644
 Estrogen pathway of 643-644
 Estrogen 67 643
 in bile 81
 effect of liver on 643-644
 Ethionine 33 18
 Ethionine 196 398 399 633
 administration of 253 495
 chronic 33
 regeneration by 90
 Ethionine induced hepatocellular injury 737
 Ethyl chloride 401
 Ethylalcohol 593
 Ethylene dichloride 394 400
 Ethylene glycol 400
 Etoglobulin 316 322
 Fcvtet on pathway of 85
 Exhaustion 101-102
 Eogenous pigments bismuth 20
 cassiterite 20
 malachite 20
 schistosomes 20
 silver 20
 Experimental hepatic injury 391-398
 Extrahepatic bile ducts 106-108
 carcinoma of 614-615
 cyst dilatation of 637
 function of 116
 gross anatomy of 106-107
 in hormonal disease of 171-172
 aberrant ducts 171
 atresia 171
 Extrahepatic bile ducts malformations of choledochal cysts 171-172
 inspissated bile syndrome 171
 of mice cystic changes in after transplantation of functional pituitary tumors 172
 microscopic anatomy of 107-108
 Extrahepatic biliary obstruction 23-237 733
 bacterial infection 235
 cirrhosis formation 235
 bile duct dilatation 232 235
 in carcinoma at bifurcation of hepatic duct 232
 causes of 189-193
 accidental surgical interruption of common or hepatic duct 191
 atresia 193
 foreign bodies 193
 invasion of biliary epithelial cells in vitamin A-deficient rats 193
 mucous plugs 193
 parasites 193
 peritoneal adhesions 193
 spasm 193
 stenosis from inflammation in neighboring organs 191 193
 stones 190-191
 strictures 191
 tumors 189-190
 classification of 488
 connective tissue alterations 235
 edema of portal tract 235
 experimental observations on in guinea pig 232
 in hepatic-duct ligation in rabbits 232
 in rats 232
 hepatic-cell necrosis 232
 hepatic injury from 465-472
 inflammation 235
 mechanical factors in 735
 recovery from 235 237
 after relief of 235 237
 successful relief of 663
 total serum bilirubin in 355
 Extrahepatic cholestasis 199-193
 bile pigment metabolism 183-189
 incomplete or intermittent 664
 and intrahepatic cholestasis differentiation between 665-666
 extrahepatic collateral development of in animals 141

F

- Faceting 299
 Factor 3 deficiency 499
 Factor V 44
 Factor VI 44
 Factor VIII 43 19 221 334
 and vitamin K 43
 Falciform ligament 167
 Fanconi's syndrome 339
Fasciola 563
Fasciola gigantica 57

- Gallstones sequelae of internal biliary fistula 303-304
obstruction of common duct 303
- Gamma fraction 317
- Gamma fraction 317
- Gamma globulin 281
- Gamma globulin 41 238 281
317 323 733
determination of 319-321
evaluation of 321
methods of turbidimetric method 3-0
procedure in 320
reagents for 3-0
technique in 3-0
physiologic basis of 319
results of 320-321
effect of on immunity to viral hepatitis 41-416
use of during epidemics of viral hepatitis 419
- Gamma globulin concentration normal 320
- Gamma globulin formation liver in 100
plasma cells during 99
- Gamma globulin fraction 99
- Gamma globulin level in chronic viral hepatitis 3-0
in cirrhosis 320
in extrahepatic cholestasis 321
in postnecrotic cirrhosis 321
in viral and toxic hepatitis 320
- Gargoylism 545
- Fatty liver in 253
- Gas bacillus infections of liver 407
- Gastric acid and intestinal motility alteration of 630
- Gastric artery left ligation of 291
- Gastric emptying 630
- Gastric juices bilirubin in 198
- Gastric motility 630
- Gastric resection high 291
- Gastrosis atrophic 630
- Gastrointestinal carcinoma 632
- Gastrointestinal diseases nonspecific reactive hepatitis in 405
- Gastrointestinal hemorrhage massive 630
- Gastrointestinal tract diffuse bleeding from in cirrhosis 290
influence of liver on 630
and liver relation between 630-632
- Gaucher's disease 544-545
- Ghost lobules 211 256 447
- Giant cells multinucleated 735
- Giardia lamblia* 571
- Giemsa stain 11
- Glanders 564
- Glaucobulin 72
- Globin 44 71 74 76
- Globulin 318
human immune 414
13 per cent 322
- Globulin formation 99-100
- Globulin level 238
- Glomerular filtration reduced 294
- Glomerulitis toxic 648
- Glomerulonephritis 648
- Glucagon 31 640 739
- Glucocorticosis 27-28 31
from fat 27
from protein 27
- Glucose 27 30
liver releasing 31
liver taking up 31
- Glucose phosphate 25
- Glucose 1 phosphate 30
- Glucose 6 phosphatase 47
- Glucose 6 phosphate 30
- Glucose tolerance abnormal associated with fatty metamorphosis 254
- Glucose tolerance test blood sugar response to hormone administration 344
to epinephrine 344
to glucagon 344
to insulin 344
results of 344
- Glucuronic acid conjugation with 68
- Glucuronidases histochemical demonstration of 46
- Glutamic acid 26
administration of 2-3
- Glutamine 27 217 2-3
urinary excretion of 45
- Glutathione 27
- Glycerol 25
- Glycine 25 27 28 67 68 73
- Glycocholate 64
- Glycocholate bile acids 63
- Glycocholic acid 27 81
- Glycoxyamine 38
- Glycogen 11 18 25 27 30 169
absence of in biopsy specimens 174
amount of 18
depletion of 18
distribution of 18
diurnal variations of 18
effect of irradiation on 656
hepatic in diabetes 640-641
histologic appearance of 18
location of in cell 18
nuclear 22
in nuclei characteristic feature of diabetes 64-
particles of 18
in recognition of sudden death 174
reduced effect of on color 18
and phosphorus poisoning 18
on resistance to poisons 18
on size 18
in regenerating liver 92
storage sites for 18
- Glycogen deposits 27
- Glycogen storage 28
in heart 543
in liver clinical features in 543
laboratory findings in 543
structural alterations in 543
- Glycogen storage disease 542-543
hepatic varieties of 544
pathogenesis of 542-543
- Glycogenesis 30
- Glycogenolysis 30-31
- Glycolysis 25 27 30 733
- Glycoproteins 316 334
- Gmelin reaction 72
- Gmelin Rosenbach test for determination of bilirubin in urine 358
- Gold colloidal 396
radioactive 657-658
- Gold therapy 401
- Gold apparatus 21
effect of vitamin C on 58
as site of formation of bile pigment 84
- Gomori's stain 11
- Gonads changes in in clinical hyperestrogenism 644
- Gonococcal hepatitis 407
- Graham Cole test for visualization of gallbladder 374 375
- Gram stain 11
- Granule fraction large 20
- Granulomas allergic from sulfonamides 402
eosinophilic 625
formation of in schistosomiasis 575
hepatic differential diagnosis of 567-568
in various diseases 564-565
intrahepatic 241-245
- Granulomatous diseases of liver 551-568
- Granulomatous lesions parasites producing 568
- Green hue of skin in prolonged biliary obstruction 75
- Grooves in liver 163
- Gross inspection 9
- Ground substance interfibrillar 94
- Growth hormone 636
- Guaiacol 63
- Guanoacetic acid 39 253
- Guanine 16
- Gummas hepatic and hepatic lobatum 564
clinical manifestations of 564
structural alterations in 564
- Gynecomastia 504 644
- II
- Hair distribution changes in in clinical hyperestrogenism 644
- Halogenated benzenes 67
excretion of as ethereal sulfates 63
as glucuronates 63
- Hematomas 262-263 587-591
bile duct 587-589
(See also Cysts hepatic)
- definition of 587
of gallbladder 591
origin of 587
solid or mixed clinical significance of 589
histologic characteristics of 589
nomenclature of 589
(See also Hemangioma)
- Hand Schüller Christian disease 545

Fibrosis pancreatic 63-
periductular 232 261 270 272
278
peribubular 443
as sequela of fatty metamorpho-
sis 254
sibica 289
Fibroxanthomatous cirrhosis 545
Fick principle of blood flow 137
Fissures 259 263
stress 259
Fixation 9 10
Fixation time 10
Fixatives absolute alcohol 10
Carnoy's solution 10
cellidin 10
chilled acetone 10
paraffin 10
Ziehl solution 10
Flatulence 219
Flatulency in nregrm 1 d 572 573
segmented 575
Flacculation 17 m 1 330
Flocculation profile 332
Flocculation tests 323-332
Flocculation test 1 (see Cephal-
in ch le te oil-flocculation
test)
colloidal gold- 330-331
coordination of 331-332
magnesium chloride 330
Flord cirrhosis 198 510-513 5-8
clinical and laboratory findings
in 510-511
differential diagnosis of 511 513
fatal 510-511
nonfatal 511
structural changes in changes in
other organs 511
histologic change 511
macroscopic appearance 511
Fluid balance in disease 62
Fluid density 163
Fluorescein 85 199
Fluorescence microscopy for d m
on transduction of vita-
min A 12
for demonstration of porphyrins
12
for visualization of collagen 12
for visualization of fat 12
Focal lesions found by biopsy ex-
amination act noncyosis 354
bucculosis 354
carcinomas 354
erythema nodosum 354
histoplasmosis 354
miliary tuberculous 354
sarcoidosis 354
syphilis 354
Folic acid 57-58
in methionine 35
in methionine 35
Follicle of sarcolemmal cycle f
557 559
matu e 557
Food intake producing tempo-
rary rise in portal pressure 286
Foreign bodies in biliary pass-
ages 655
Formaldehyde 10
Formic acid 25 27
Formol gel test 331

Foulet's reagent for determination
of bilirubin in urine 353
Fowler's solution 401
Fraser partition theory of 33
Fructokinase 31
Fructose 30 344
Fructose metabolism 31
Fructose 1-phosphate 31
Fumarate 25
Fungus 110
Fungus infections of liver 565-
567

G

Galactokinase 31
Galactose 30
Galactose diabetes 543
Galactose index 345
Galactose metabolism 31-32
Galactose-1-phosphate 31
Galactose in normal constant
(GRC) 345
calculation of 346
technique for 346
collection of sample 346
determination of galactose
346
reagents in 346
Galactose time 345
Galactose tolerance test 345-347
Calculation of 347
methods of 345
determination of galactose in
blood 345
galactose clearance 345-346
(See also Galactose-remo-
val constant)
urinary excretion 345
physiologic basis of 346
results of 346-347
in thymic tissue 346
Galactosemia 543-544
Clinical manifestations of 544
pathogenesis of 543-544
spontaneous 345
structural alterations in 544
Galactose 345
Gallbladder 110 111-
aberrant bile ducts in 112
abnormal absorption by 116
absorption of bile salts by 116
absorption of electrolytes by
116
adenomatous of 591
anatomy without 110
capacity of 110
carcinoma of (see Carcinoma of
gallbladder)
concentration of bile in 115-
116
contracted 306
dilatation of 112
effect of intestinal tract on 632
function of cystic duct in 115
functions of expulsion of bile
113
storage of bile 113
gross anatomy of 110
lamination of 591
lithiasis of 303 308

Gallbladder inflammatory pseudo-
diverticulum in 112
malformations of anomalies
173
biliary 173
bilobed 173
complete absence of 173
diverticula 173
histologic gastric mucosa
173
lithiasis gallbladder 173
lymphatic 173
pharyngeal cap 173
reduplicated 173
symptoms of 173
malpositions of 173
cystic duct ligament 173
mucosal expulsion pressure ex-
erted by 114
macroscopic anatomy of 110 112
in the glands of 112
nerves to 153
pressure regulation by 116
reabsorption of bile to 115
secretion by 116
and spectrum of Oddi's antago-
nistic innervations of 117
interrelation between 117-119
cholekinetic drugs 119
effect of cholecystectomy
119
hormonal stimulation 117
nervous stimulation 117-
118
reflux between pancreatic
and biliary ductal systems
119
stimulation by foods 119
strawberry or lumpy 306
torsion of 305
Gallbladder bile 80
Gallbladder contractility 113-115
abnormal variations in 115
phases of 114-115
physiologic variations in 115
in pregnancy 115
rhythmic contractility 113-114
spontaneous 115
a minute pulse in 115 118
Gallbladder disease in diabetes
643
Gallbladder lymphatic vessels 150
Gallbladder mucosa 80
Gallbladder syndromes 293-309
interdependence of 303-309
postcholecystectomy syndrome
308-309
Gallstone formation 299-304
processes operating in 300
(See also Gallstone Stone for-
mation on Stones)
Gallstone ileus 304
Gallstones ductal production of
736
incidence of 301
physiologic phenomena character-
istic of 299
sequelae of 303-304
carcinoma of gallbladder
304
cystic duct obstruction 303
dyskinesia 303
inflammation 303

- Hepatic artery intrahepatic portion of larger vessels** 125
 left 122
 ligation of 125 143 291
 in cirrhosis 143
 in dogs 143
 and cats 143
 site of 143
 middle 122
 radicular branches of 136
 and regeneration 93
 right 122
 terminal distribution of 125
 variations of 122 124
 accessory 124
 displaced 122
- Hepatic artery blood flow** 143
 incomplete obstruction of 143
 interruption of 143-145
 anemic infarcts 143-145
 in animals 143
 ligation of hepatic artery 143
 in man 143
 relation of to portal vein 139
- Hepatic artery occlusion** 145
- Hepatic artery system sphincters** in 146
- Hepatic bile** 80
 physical characteristics of 80
 81
- Hepatic blood flow in cardiac failure** 139
 in cirrhosis 138 282
 estimated 137
 in experimental ischemia 139
 in fatty livers 139
 in hemorrhage 139
 in hyperthyroidism 139
 regulation of 146-148
 after splenorenal or portocaval shunt operations 139
- total** 137-139 734
 abnormalities in 138-139
 measurement of methods of 137-138
 pharmacologic influences on
 acetylcholine 138
 alcohol 138
 anesthesia 138
 bile acids 139
 cinchophen 138
 epinephrine 138
 hexamethonium 138
 norepinephrine 139
 physiologic influences on
 blood pressure 138
 eating 138
 exercise 138
 pregnancy 138
 stimulation of vagus nerve 138
 sympathetic nerve tone 138
 upright position 138
 variations in sinusoidal blood flow throughout lobule 139
- Hepatic blood vessels function of** 137-148
 structure of 122-136
- Hepatic calculi** 301
- Hepatic capsule** 154
- Hepatic cell degeneration** 197
 chemical changes in liver in 213-214
 in cholestasis 225 227
 after relief of obstruction 227
 serum and urine in chemical changes in 215-219
- Hepatic cell functions** 24
- Hepatic cell nuclei changes in following single toxic injury** 736
- Hepatic cell plates concept of** 103
 discontinuity of 182
 disruption of 189
- Hepatic cells adult growth of** 87-88
 arrangement of limiting plate 14
 one cell thick plates 14
 cell membrane of 14
 shape of 14
 size of 14
 structure of 14-23
- Hepatic cholesterol (see Cholesterol)**
- Hepatic circulation development of** 166-167
 vital microscopic observations of 135-138
- Hepatic degeneration diffuse** 396
- Hepatic disease in left lobe** 734
 in parallel involvement of pancreas and liver 633
- Hepatic diseases classification and nomenclature of** 389-390
- Hepatic diverticulum** 165
- Hepatic duct common right and left main branches of** 106
 main 106
 one main obstruction of 184
- Hepatic epithelial cells transformation of into mesenchymal elements** 734
- Hepatic excretory reserve limits of** 182
- Hepatic failure and renal injury correlation between** 650
 severe indication of 667
- Hepatic injury congestive (see Congestive hepatic injury)**
 from disturbed circulation and anoxia 482-492
 experimental 391-398
 from extrahepatic biliary obstruction 468-472
 human from congestion 474-481
 from infectious agents classification of 413-414
 from internal irradiation 657-658
 metabolic (see Metabolic hepatic injury)
 morphologic brain changes in 652
 in nonjaundiced patients demonstration of 667
 nutritional (see Nutritional hepatic injury)
 toxic (see Toxic hepatic injury)
 traumatic 654-655
- Hepatic injury and tuberculosis relation between** 556
- Hepatic insufficiency clinical manifestations of** 219-224
 degree of appraisal of 667
- Hepatic involvement incidence of** 454
- Hepatic lymph amount of** 150-151
 constitution of 151
 flow of 151
 and ligation of common bile duct 151
 production of 151
 increased ascites in 295
 protein in 151
 protein concentration of 151
- Hepatic manifestations clinical** 454
- Hepatic necrosis** 69 735
 in eclampsia (see Eclampsia hepatic necrosis in)
 extensive in maternal hepatitis 459
 portal hypertension caused by 284
 from shock 482-483
 functional hepatic changes in shock 482-483
 circulatory effects 482-483
 clinical consequences 483
 metabolic effects 483
 mechanisms contributing to 482
 structural changes in 483
 experimental shock 493
 human shock 483
- Hepatic nerve plexus anterior** 152
 posterior 153
- Hepatic pain** 153
 during biopsy 153
- Hepatic and plasma vitamin A levels** 238
- Hepatic response to stress** 654-655
- Hepatic side reactions** 402
- Hepatic tests** 313-314
 classification of 314
 physiologic classification of 314
 sensitivity classification of 314
 principles of 313-314
 screening in preicteric period of acute viral hepatitis 425
 (See also Tests)
- Hepatic vasodepressor material (see VDM)**
- Hepatic vein** 133-135 145 167
 complete experimental obstruction of 145
 diseases of 593
 extrahepatic portion of 133-134
 intrahepatic portion of 133
 microscopic anatomy of 113
 large blood pressure in 145
 microscopic structure of 133
 muscular throttle mechanism of in animals in 134
 occlusion of 481
 partial obstruction of 145

- Hanser 163
Harrison test for determination of bilirubin in urine 353
Hartmann's pouch 110
Hays test for determination of bile acids in urine 365
Heart failure as it is 295
 circling and nuclear glycosogen 22
Heist run valve 115
Helmholtz's statistics of liver 572-588
Hemangioendothelioma 591
Hemangio-myx 539-591
 classification of 591
 clinical significance of 591
 diffuse hepatic angiomas 591
 histologic appearance of 591
 of liver biopsy or a paragon of 739
 structural characteristics of 539-591
 tongue-like 644
Hematemesis rupture of varix as cause of 290
Hematin 72-74
Hematin globin 74
Hematoidin 179
Hemolytic disorders incidence of upon liver 649
Hematologic findings in acute viral hepatitis 425
Hemolytic structures abnormal in liver 624-635
Hemolytic hepatitis 624
 fetal 624
 portal 624
 bone marrow replacement in 624
 necrosis in 624
 in myeloid metaplasia 624
Hematopoietic system effect of liver on 627-629
 effect of on lymphoid elements 629
 on segmented leukocytes 628-629
 on thrombocytes 628
 influence of upon red cells 627-628
 and ileo-portal involvement of 629
 relation between 624-627
 and spleen relation of liver to 623-629
Hematoxylin 72-79
Hematoxylin-eosin stain 10
Heme 71-72-74
Hemoglobin 72
Hemoglobin 70
Hemochromatosis 19 532-535-540-633
 cardiac 610
 cardiac element in 535
 causes of death 535
 clinical manifestations of 535
 erythrocytosis in 539
 exogenous 532-539
 hemolysis 538-539
 Sheldon's theory of 538-539
 artificialities of 538
Hemodematosis incidence of 535
 iron in 61-101
 irritating effects of iron deposition in 269
 laboratory diagnosis of 539
 leucosiderin in epithelial cell in urinary sediment 539
 iron pigment in gastric mucosa 539
 laboratory findings in 535-539
 iron-binding capacity of serum 536
 serum iron level 536
 lower incidence of in women 539
 morphologic alterations in 536-539
 biopsy findings 536-539
 cancer formation 536
 changes in other organs and renal cortex 539
 intestine pituitary 539
 bone marrow 539
 chronic pleurisy 539
 gastric and duodenal mucosa 539
 heart 538
 hemofuscin 538
 intestinal villi 539
 kidney 538
 lymph nodes 539
 muscle 538
 pancreas 538
 parathyroid 538
 pigments in skin 539
 salivary glands 538
 skin 538
 spleen 538
 testes 538
 thyroid 538
 chemical analysis 538
 histologic changes 538
 macroscopic appearance 538
 secondary 532
 associated with anemia 539-540
 clinical manifestations of 540
 iron distribution in 540
 pathogenesis of 539-540
 role of anemia 540
 role of blood transfusions 539
 role of redistribution of iron 539-540
 recovery in 540
 structural alterations of 540
 excess on absorption and storage in 733
 treatment of 539
Hemodilution 224
Hemofuscin 19 538
Hemoglobin 27-70-71
 synthesis of 72-74
Hemoglobin birefringence in 74-75
Hemolysis factors causing 182-188
 hepatocellular degeneration from 488-491
 antibacterial 74
 in liver diseases 289
Hemolytic anemia congenital and acquired 488
 erythroplagiasis in 99
Hemolytic disease of the newborn 483-491 585
 histologic findings in 489
 excessive erythropoiesis 489
 fibrosis 489-491
 functional changes 489
 macroscopic appearance of 489
Hemolytic effect of ingested fat in milk 186
Hemolytic index 363
Hemorrhagic coma and death following cause of 738
 from esophageal varices 133
 massive gastro-intestinal 630
Hemorrhagic diathesis 581-219-221
Hemorrhagic manifestations with retractor of fibrinogen 43
Hemorrhagic renal changes in hypotrophic deficiency 649
Hemorrhoids 133
 in cirrhosis 290
Hemorrhoids 19-20-39-61-74-539
 in epithelial cells in urinary sediment 539
Hemorrhoids 101-239-532
 hemorrhoids vs 535-539
 (See also Siderosis)
Hemorrhoids and hepatic gummata clinical manifestations of 584
 structural alterations in 584
Hemorrhoids 219
Hemorrhoids animals 37
Hemorrhoids hypoglycemia as early effect of 31
 partial 41-88
 nucleolus after 23
 regeneration after 22
Hemorrhoids oxygen difference 145-146
Hepatic artery 122-127 143-145
 anastomoses of with phrenic artery 125
 aneurysms of 145
 diseases of 581-583
 aneurysms of hepatic arteries 581
 arteriosclerosis 581
 arteriosclerosis 581
 diminished portal thrombosis 581
 hypersensitivity angitis 581
 lupus erythematosus 581
 obliterating thromboangiitis 581
 polyarteritis nodosa 581
 entire extirpation of in monkeys 143
 irreparable portion of 122-125
 interhepatic portion of 125-127
 interlobular arteries radicular or vascular branches 125
 interlobular arterioles 125
7

- Hepatocellular degeneration nutritional fatty liver with (see Nutritional fatty liver with hepatocellular degeneration)
principal alterations of 200 202
serum bilirubin level in 187
- Hepatocellular injury in rats fed human diets 73
- Hepatocellular insufficiency 184
- Hepatocellular iron in brown atrophy 20
in cirrhosis 20
in fatty metamorphosis 20
in nutritional deficiencies 20
in pancreatic disease 20
- Hepatolenticular degeneration (see Wilson's disease)
- Hepatolenticular relationships 623-624
- Hepatoma 589 597
formation of as sequelae of fatty metamorphosis 254
- Hepatomegaly during amebic enteritis 569
in children differential diagnosis of 668
in juvenile diabetes 642
in nonjaundiced patient differential diagnosis of 667-668
■ presenting feature of metastatic tumors of liver 617
- Hepatosplenic 170
- Hepatorenal relationships 647-651
common functions 647-648
excretory functions 647
metabolic functions 647
vasoregulatory functions 647
common injuries 648
influence of kidney on liver 650-651
influence of liver on kidney 648-649
(See also Renal function in liver disease Renal structural changes)
- Hepatorenal syndrome 650
- Hepatitis hepatitis vs 389-390
serous 259 519
- Hepatosplenopography 377
- Hering canal of 103
- Hering's concept of sinusoids 94
- Herpes simplex hepatitis 458
- Herrlicher 120
on morphology of degeneration 88
- Heterochromatin 18
- Heterotopic gastric mucosa 173
- Hexokinase 30
- Hexokinase system 30
- Hexose monophosphate shunt 25
27 31
- Hilus of liver 160
- Himsworth 262
- Hippuric acid 27 67 68
- Hippuric acid formation 57
- Hippuric acid synthesis 233 368-379
evaluation 369
method of 368
- Hippuric acid synthesis paraaminohippurate synthesis 369
physiologic basis of 368
results of 369-369
in liver disease 369
- Histamine 83 119 147
increasing portal pressure 286
- Histamine wheals 193
- Histidine 28
urinary excretion of 45
- Histiocytes 97 154
portal and Kupffer cells proliferation of 241
- Histiocytic and lymphocytic cells accumulation of 154
- Histochemical reactions 11
- Histologic specimens 10
- Histones 21
- Histoplasmosis 241 565
diffuse septal cirrhosis 565
granuloma formation in 565
Kupffer cell invasion 565
- Hodgkins disease 241 565 625
Hoffbauer 181
- Homeostatic regulation 31
- Homocysteine 27
- Homocystine 38
- Hormonal factors 399
- Hormones antidiuretic 636
corpus luteum influence of liver on 645
excess in ascites 294-295
gonad stimulating 636
growth 636
posterior pituitary 636
thyrotropic 636
- Horse liver anaerobic bacteria in 99
- Howe method of determination of serum albumin 318
- Howell 219
prothrombin time of 335
- Humoral stimulus for regeneration 92
- Hunger increasing bile flow 83
- Hyalinization 202
- Hyaluronidase inhibiting principle 50
- Hyaluronidase inhibitors 282
- Hydatid disease 575-578
clinical manifestations of 578
alveolar echinococcus 578
578
anaphylactic shock 578
atrophy of left lobe 578
bile duct infection 578
carcinoma of liver 578
hematogenous dissemination 578
infection 578
jaundice 578
rupture of cysts into various organs 578
geographical distribution of 575-578
Laboratory findings in 576
structural alterations in 576-578
fertile stage of encystment 576 578
formation of exogenous daughter cysts 578
- Hydatid disease structural alterations in inflammation and around cysts 578
stage of migration 576
sterilization of cysts 578
- Hydatid fluid 147 576
- Hydatid sand 578
- Hydrochloresis 82
bile acids during 83
bile pigment during 83
cholesterol during 83
in hepatic congestion 83
- Hydrocortisone 638
- Hydropic degeneration in bromobenzene intoxications 203
in carbon tetrachloride intoxications 203
in chloroform intoxications 203
etiology of 203
histochemistry of 203
morphology of 203
in prolonged extrahepatic cholestasis 203
in viral hepatitis 203
balloon cells in 203
- Hydrops of gallbladder 303 305
- Hydrops fetalis 458
- Hydroxyproline 28
- Hyperbilirubinemia persistent 445-446
- Hyperestrogenism 290
clinical 644-645
changes in gonads 644
changes in hair distribution 644
changes in prostate gland 644
gynecomastia 644
palmar erythema 645
spider nevi 644-645
uterine carcinoma 644
- Hypergammaglobulinemia 99
- Hyperlipemia phospholipids in 36
- Hyperplasia 645
coarse nodular 286
multiple nodular 449
- Hyperpotassemia and sodium 59
- Hyperreflexia 23
- Hyperresponsivity 659
drug reactions as cause of intrahepatic cholestasis 198
- Hypersplenism 289 623
- Hypertension arterial in cirrhosis 631
in liver diseases 647
malignant arteriosclerosis in 581
portal (see Portal hypertension)
- Hyperthyroidism effect of on liver 484
- Hypertonic glucose and bile flow 83
- Hypertrophy of bile ducts 645
- Hyperstamiosis ■ 55
- Hypoacidity 630
- Hypoalbuminemia 42 294
- Hypochromasia 628
- Hypophemia 222 640
as early effect of hepatectomy 31
fasting 215
in human liver disease 31
spontaneous 344

Hepatic vein subacute obstruction
of in man 145
symptoms of 145
Hepatic vein branches and portal
vein branches anastomoses
between 366
Hepatic vein catheterization 137
Hepatic vein flow interference
with 145
Hepatic vein-hepatic artery anas-
tomosis 136
Hepatic vein obstruction and re-
generation 93
Hepatic vein splinters 146-147
in dog 147 151
in reply of 147
in various animals 134-135 147
Hepatic vessels injected in prepara-
tions of 136
Hepatic vein in A and serum
vitamin A relation between
55
Hepatitis acute 733
and cirrhosis differential di-
agnosis between 666
protein bound iodine 217
acute amebic 589-590
acute cholangiolitic 433
acute icteric jaundice period
of 423
prodromal period of 423
in adult secretory 407
anterior 423-424
lactation 407
biliary (see Biliary hepatitis)
caused by infection mononucleosis 454-455
in child 424
cholestatic 424
chronic 446
chronic toxic (see Fibrosis cir-
rhosis)
cirrhosis with jaundice 531
clinical course of factors in indi-
vidual 424
alcoholism 424
in child 424
malignant 424
other diseases 424
pregnancy 424
cytomegalic inclusion 456
in diabetes 643
fatal or fulminant epidemic 414
fulminant 434-436
giant-cell 460-462
clinical manifestations of 460
structural alterations of 460
transition of into primary he-
patic carcinoma 738
gonococcal 407
with hepatic failure 424
vs hepatitis 389-390
herpes simplex 436
infected biliary 435
filtrative 425 404
leptospirosis (see Weil's disease)
in biopsy in 383-394
malignant 458-459
malignant 446
neonatal 171
neonatal giant cell 738
on specific granulomatous 559

Hepatitis nonspecific reaction
156 404-407 551 737
clinical and laboratory find-
ings in 404 405
diffuse systemic diseases
lupus erythematosus 405
nonspecific febrile reac-
tions 405
rheumatic fever 405
rheumatoid arthritis 405
systemic nodular pannicu-
litis 405
etiologic factors in 405-407
in gas bacillus infections 407
in gastrointestinal diseases in
gallbladder disease 405
in gastrointestinal cir-
rhosis 405
in peptic ulcer 405
in ulcerative colitis 405
in pneumonia 405 407
in rickettsial diseases 407
in sclerosing 575
structural changes in 405
in surgical biopsy specimens
404
in viral diseases poliovirus
407
smallpox 407
varicella 407
pernicious 424
pernicious 184
persistent anicteric subicteric
or icteric spotty necrotic
441-442
clinical features of 441
laboratory findings in 441
structural changes in 441-
445
formation of collagen mem-
branes and regenerates
nodules 443
functional correlation of per-
sistent histologic changes
443 445
incidence 445
persistent ductular changes
443
persistent mesenchymal
changes 443
persistent portal and peri-
portal changes 443
persistent spotty necrosis
441 443
residual collapse 443
portal 445
postoperative toxic 411-412
clinical features of 411
pathogenesis of 412
structural alterations of 411-
412
posttraumatic 420
incidence of 420
fractured factors responsible
for 439-440
incubation of biopsy find-
ings 440
persistence of virus 439
persistent anicteric
changes 439
persistent symptoms 439
clinical 440

Hepatitis protracted factors re-
sponsible for sequelae
various incidence of 440
severe acute stage 439
types of 440-453
protracted mass necrotic
form of 446-449
changes in other organs in
brain changes 449
erosive gastritis 449
esophageal varices 449
hemorrhagic tendencies
449
marrow hyperplasia 449
peptic esophagitis 449
splenomegaly 449
clinical features of 446
histologic changes in 447-
449
collapse 447
ductal and inflammatory
changes 447
glomerulules 447
necrosis of hepatic cells
447
regeneration 447 449
stress fissures 449
laboratory findings in 448
macroscopic appearance of
446-447
morphogenesis of 449
prevalent 445
recurrent 445
Rift Valley fever 456
salmonella 407
serous 440 459
serum 414
prophylaxis of 420-421
(See also B virus hepatitis)
serum alkaline phosphatase in
341
spotty necrotic cirrhosis from
446
streptococcus 407
subacute in adolescent girl
738
subicteric 423
syndrome or instrument trans-
mission of 419-421
transmission of in vitro 424
urobilinogen in urine in 381
ral (see Viral hepatitis)
yellow fever 455-456
Hepatoblastoma 610
Hepatobiliary fistula 571
Hepatocellular degeneration 187
200-205 235 280-281
bile pigment metabolism in 187
bilirubin in urine in 187
in biopsy specimen 200
from hemolysis 488-491
by irregularities of arrangement
of cells 200
and necrosis functional altera-
tions of 155-224
mechanisms of circulatory
factors 214
deficiency factors 214
inflammation and infection
214
toxic factors 214
nuclear alterations of 200

- Irradiation** external specific effects of on hepatic structure or composition enzymes 656-657
glycogen 656
iron 657
lipids 656
phosphorus 657
structural changes 656
internal hepatic injury from 657-658
plutonium 657
radioactive gold 657-658
radioactive phosphorus 658
radium and thorium 657
- Isoleucine** 26
- Isoniazid** 402
- Ivy** 298
- J**
- Jaundice** 179-199
absence of in severe hepatic injury 182
adynamic 181
antisyphilitic treatment 419
bradycardia in 651
catarrhal 414
chlorpromazine 404 737
cholangiolitic 181
in cholangitis 193
chronic intermittent juvenile 186
in cirrhosis 526
cirrhosis without recognition of 531
classification of according to existing theories 179-181
in congestive hepatic injury 738
convalescent serum 420
differential diagnosis of 664-665
basic principles in 664
exceptions to 664
liver biopsy in 384
dynamic 181
early theories of 179
emotional disturbances producing or aggravating 185
in enlargement of portal lymph nodes 189
Eppinger's theory of 179-180 182
existing theories of criticism of 181-185
familial nonhemolytic 181 186
in heart failure 474 477
hemolytic (overproduction) 185-186
in hemolytic disease of the newborn 489
in hepatectomized geese 179
hepatocellular 181
hepatocellular 181
feter hepatitis in 221
in Hodgkin's disease 189
with impairment of bile flow 187-198
without impairment of bile flow 185-186
from intrahepatic lesions 197
cholangiolitis (see Cholangiolitis)
- hepatic cell degeneration 197
in leukemia 189
- Jaundice lymphogenous** 181
in lymphomas 189
McVee's classification of 180
medical and surgical laboratory differential diagnosis of outline for 664-665
in metastases to portal lymph nodes 189
in metastatic tumors in liver 617 619
methyltestosterone 183 403-404
neonatal 186 197-198
as cause of intrahepatic cholestasis 196
classification and differential diagnosis of 198
differential diagnosis of 665 (See also Hepatitis giant cell)
- nonhemolytic retention 186-187
obstructive 180
in pancreatitis 633
following paraaminosalicylic acid treatment 404
parenchymatous 180
Javal's theory of 180-181
period of in acute icteric hepatitis 423
physiologic 186
in porphyria 79
posthepatic 187
in prematurity 186
production 181
proposed classification of 185-187
practical application of 196-198
regurgitation 180
retention 180
Rich's theory of 180
in septicemia 407
as sequela of trauma 655
sphincter of Oddi spasm causing 299
spirochetal 457
surgical and medical 197
secondary hepatic cell degeneration in 664
tissue discoloration in 198
total serum bilirubin in 355
in tuberculosis 189
in tumor metastases 184 193
visible 198-199
With's theory of 181
yellow fever vaccine 419-420
functional veins dilatation of 290
- K**
- Kala-azar** 241
- Karsner** 262
- Kernicterus** 199 489 652-653 665
clinical features of 652
diseases associated with 652
pathogenesis of 65-653
ketocolic acidosis 83
ketogenesis 25-29
in hepatic injury 735
ketone bodies 25
keto 29
in experimental liver damage 29
- Ketosis** in liver disease 29
- Kidney** influence of on bile pigment excretion 650-651
on liver 650-651
influence of liver on 648
relation of liver to 647-651
role of in dye excretion 85
- Kjeldahl** 315
- Krebs cycle** 733
and mitochondria 21
- Krebs-Hensleit cycle** 27
- Krebs tricarboxylic acid cycle** 27
- Kupffer cell fat** 251
- Kupffer cell-hepatic cell block** 187 188
- Kupffer cell mobilization** diffuse 240
- Kupffer cells** antibodies formed by 99
in blood pigment breakdown 101
dye excretion in 85
fat content of 100
fat storage in 100
in Cruchers and Niemann's sick disease 100
in Hodgkin's disease 100
iron in 61
iron storage in 101
metabolic function of 100-101
as part of reticuloendothelial system 97-98
phagocytic activity of 12
phagocytosis of colloidal material by 734
and portal histiocytes proliferation of 241
role of in bilirubin 77
and sinusoids 94 96
vs endothelial cells 96
inclusions in 96
in typhoid fever 441
stain A in 100-101
- Kwashiorkor** 516 518
adult 518
juvenile 518
- Kynurenine** 57
- L**
- Lactate levels** 223
- Lactic acid** 25 30
- Lactic acid tolerance test** 347
- Laennec's cirrhosis** 278-279 446
520-523 600-603
biopsy specimens of 527
- Lancet fluke** 573
- Lead** 394 401
- Leclithin** 33 34 37
- Lectinase** 49
- Leiomyosarcoma** 618
- Leishmaniasis** 459
- Leptospirosis** 515
- Leptospirosis** 628
- Leptospira canicola** 459
- Leptospira icterohemorrhagiae** 457
- Leishman space-occupying reaction** of 666
- Letterer-Siwe disease** 625
- Leucine** 28 28 45 218 495
urinary excretion of 45

- Hypophysectomy 35 635
functional alterations in 635
structural changes in 635
Hypoparathyroidism 219
Hypoproteinemia 304
as sequelae of a disease 298
Hypoproteinemia 43 220
in experimental animals 43
with faulty response to vitamin K 220
in hepatic cirrhosis 43
in hepatic diseases 43
idiopathic 221
Hypothymia 655-656
Hypoalbuminemia effect of on liver 473
- I
- Icterus index 354
results of 354
Icterus neonatorum 181 186
anthracosis in 199
Icterus sphyllus praecox 562
Idiopathic hypoparathyroidism 221
Idiopathic porphyria 79
Idiosyncrasy 401-402
IH virus 414
Indinavir injection of blockade
following toxic factor 101
in Kupffer cells 101
in plasmacytosis 98
Indole metabolism of as ethereal
sulfate 100
Infantile sclerosis 518-519
Inflammation 238 240-243
from anoma of gallbladder
301
in urticaria 281
in granuloma 305
from non-specific colicystitis
301
in papilla of Vater 245
periparturient 24 245
periparturient non-specific forms of 245
and periparturient 243 245
etiological factors in 242
245
functional significance of
245
morphogenesis and localization of 242
in juvenile 245
specific forms of in acute
urinary pathosis 245
in granulomatous diseases
445
structural changes in 245
from salmonella infection 301
as sequelae of gall disease 33
stones from in neighboring
organs as cause of extra
hepatic biliary obstruction
191 193
stones follow 301
from typhoid 301
Inflammatory duct differences
in between specimen observation and autopsy and biopsy
175
- Inflammatory reactions around
duodenal ulcers or diverticula
193
Infrared photography 131 132
290
Infundibulum 110
Injection preparations of hepatic
vessels 136
Injection techniques gross in
spectrum complemented by 11
Inner action of liver 151-154
afferent 153
function of 153-154
structure of 151-153
extrahepatic nerves 152
fibers carrying pain stimuli
153
intrahepatic nerves 151-152
nerves in biliary tree 153
pleuric nerve 153
splenic nerve 152
vagus 152
Insulin 25 35 58
Insulin 30 31 83
action of liver on 639
effect of on carbohydrate metabolism 639
on fat metabolism 639
on liver 639-640
on protein metabolism 639-640
function of 30
inactivation of 39
and potassium 59
site of action of 639 33
Inulin test 640
Inulin tolerance tests 640
Insulinase 639 739
Insulinase inhibitors 739
Intact digestion of essels 132
Intestinal bile ducts 120-121
Intestinal spices widening of in
instantaneous death 174
Intestinal absorption interference
with as sequelae of ascites 298
Intestinal motility and gastric acid
secretion of 630
Intestinal tract influence of upon
liver 630-633
Intestine modification of by
nutritional factors 500-501
Intraductal magnesian sulfate
119
Intestine bile ducts 106 113
in anoma of 613-614
malformations of atresia 170
cysts 170
Intrahepatic biliary obstruction
184-185
Intrahepatic cholestasis 184-185
193-196 29-232 684 737
bile pigment in metabolism 188 195
causes of 195-196
bacteria 196
cyst 196
hypersensitivity drug reaction 196
in neonatal jaundice 196
in 196
intrahepatic 195-196
on cholestasis 232
bile sand 232
- Intrahepatic cholestasis early 229
elevation of total cholesterol and
phospholipid level 195
etiology of 185
functional (see Cholangiolitis)
increase of serum alkaline phosphatase activity in 195
mechanical 193 197
congenital aplasia of ducts
193
pathogenesis of 195
reduction on absence of urinary
urobilinogen in 195
in acute 29 232
in hypersensitivity reactions
229
Intestinal ductules 106
Intestinal hemolysis 74
Iodine protein bound in acute
hepatitis 217
Iodipamide 376
Iodipamide methylglucamine 376
Ion exchange resins 296
Ionizing radiation 656-658
Ionizing 59-60
absorption of 60-61
and dosage of excess in secondary
hemochromatosis 63
in anemia 20
in bile 61
content of liver 60 536
distribution of 53
easily split off 75
effect of irradiation on 657
essential hepatic uptake of 61
incretion of 60-61
in bile 61
in hemochromatosis 61 101
in metabolic diseases 20
hepatolysis 20
in human malnutrition 61
as an irritant 533-534
in Kupffer cells 61
redistribution of in secondary
hemochromatosis is associated
with a 539-540
release of from liver 61
in serum and hepatic relation between 733
In administration excessive parent at 61
in peripheral organosiderosis 534
prolonged and excess 61
in distribution in secondary
hemochromatosis 540
Iron pigments 19-20
in gastric mucosa 539
PAS reaction of 20
toxic effect of 539
Iron storage in Kupffer cells 101
Iron storage as 532-540
Iron adulation trial 656-657
effects of on hepatic function
657
non-specific effect of on cell
656
specific effects of on hepatic
structure or composition
656-657
ATP 657

Irradiation external specific effects of on hepatic structure or composition enzymes 656-657
glycogen 656
iron, 657
lipids 656
phosphorus 657
structural changes 656
internal hepatic injury from 657-658
plutonium 657
radioactive gold 657-658
radioactive phosphorus 658
radium and thorium 657
Isoleucine 46
Isoniazid 402
Ivy 298

J

Jaundice 179-199
absence of in severe hepatic injury 182
adynamic 181
antisyphilitic treatment 419
bradycardia in 651
catarrhal 414
chlorpromazine 404 737
cholangiolitis 181
in cholangitis 193
chronic intermittent juvenile 186
in cirrhosis 526
cirrhosis without recognition of 531
classification of according to existing theories 179-181
in congestive hepatic injury 738
convalescent serum 4-0
differential diagnosis of 664-665
basic principles in 664
exceptions to 664
liver biopsy in 384
dynamic 181
early theories of 179
emotional disturbances producing or aggravating 185
in enlargement of portal lymph nodes 189
Eppinger's theory of 179-180
existing theories of criticism of 181-185
familial nonhemolytic 181 186
in heart failure 474 477
hemolytic (overproduction) 185-186
in hemolytic disease of the newborn 489
in hepatectomized geese 179
hepatocellular 181
hepatocellular 181
fetal hepatitis in 221
in Hodgkin's disease 189
with impairment of bile flow 187-199
without impairment of bile flow 185-186
from intrahepatic lesions 197
cholangiolitis (see Cholangiolitis)
hepatic cell degeneration 197
in leukemia 189

Jaundice lymphogenous 181
in lymphomas 189
McNee's classification of 180
medical and surgical laboratory differential diagnosis of outline for 664-665
in metastases to portal lymph nodes 189
in metastatic tumors in liver 617 619
methyltestosterone 183 403-404
neonatal 186 197-198
as cause of intrahepatic cholestasis 196
classification and differential diagnosis of 198
differential diagnosis of 665
(See also Hepatitis giant cell)
nonhemolytic retention 186-187
obstructive 180
in pancreatitis 633
following primary biliary acid treatment 404
parenchymatous 180
Pavels theory of 180-181
period of in acute icteric hepatitis 423
physiology 186
in porphyria 79
posthepatic 187
in pregnancy 186
production 181
proposed classification of 185-187
practical application of 196-198
regurgitation 180
retention 180
Rich's theory of 180
in septicemia 407
as sequela of trauma 655
sphincter of Oddi spasm causing 299
spirochetal 457
surgical and medical 197
secondary hepatic cell degeneration in 664
tissue discoloration in 195
total serum bilirubin in 355
in tuberculosis 189
in tumor metastases 184 193
visible 198-199
With's theory of 181
yellow fever vaccine 419-420
Junctional veins dilatation of 290

K

Kala azar 241
Karsner 62
Kernicterus 199 499 652-653
665
clinical features of 652
diseases associated with 652
pathogenesis of 652-653
ketocholanic acids 83
ketogenesis 28-29
in hepatic injury 735
ketone bodies 25
Kitt's 29
in experimental liver damage 29

Ketosis in liver disease 29
kidney influence of on bile pigment excretion 650-651
on liver 650-651
influence of liver on 648
relation of liver to 647-651
role of in dye excretion 85
Kjeldahl 315
Krebs cycle 733
and mitochondria 21
Krebs-Hensleit cycle 27
Krebs tricarboxylic acid cycle 27
Kupffer cell fat 451
Kupffer cell-hepatic cell block 187 188
Kupffer cell mobilization diffuse 240
Kupffer cells, antibodies formed by 99
in blood pigment breakdown 101
dye excretion in 85
fat content of 100
fat storage in 100
in Gaucher's and Niemann-Pick disease 100
in Hodgkin's disease 100
iron in 20 61
iron storage in 101
metabolic function of 100-101
as part of reticuloendothelial system 97-98
phagocytic activity of 12
phagocytosis of colloidal material by 734
and portal histiocytes proliferation of 241
role of in bilirubin 77
and sinusoids 94 96
vs endothelial cells 96
inclusions in 96
in typhoid fever 241
vitamin A in 100-101
Kushnork 516 518
adult 518
juvenile 518
Kynurenine 57

L

Lactate levels 23
Lactic acid 25 30
Lactic acid tolerance test 347
Laennec's cirrhosis 278-279 446
520-523 602-603
biopsy specimens of 527
Lancet fluke 573
Lead, 394 401
Lecithin 33 34 37
Lecithinase 49
Leiomyosarcomas 616
Leishmaniasis 459
Leptomis miliary 565
Leptosis 565
Leptocystosis 623
Leptosira canicola 458
Leptosira icterohemorrhagiae 457
Les in space-occupying recognition of 666
Letterer-Siwe disease 625
Leucine 20 28 45 218 495
urinary excretion of 45

- Leucine crystals 338
 Leukemia 99 624-625
 lymphocytic 625
 monocytic 625
 myelocytic 624-625
 Leukocytes segmented eff of f
 hematopoietic system on 628-
 629
 Leukopenia 289
 Leukotolrance test 344-345
 method of 345
 physiological basis of 344-345
 results of 345
 Lieberman-Burke reaction for
 determination of serum cho-
 lesterol 349
 Lietzgang rings 299
 Ligaments of liver coronary lig-
 ament 160
 falciform ligament 160
 peritoneal ligament 160
 ligamentum teres 160 167
 triangular ligament 160
 triangular ligaments 160
 Ligamentum teres 160 167
 Ligamentum venosum 167
 Ligament of hepatic artery 291
 of left gastric artery 291
 of splenic artery 291
 of varices 291
 Ligula of stomach 578
 Lipase 49 633
 Lipid metabolism 32
 Lipid storage diseases in liver
 544-545
 Lipid tolerance tests 353
 Lipids 251
 Lipids 219
 alteration of in postmortal pro-
 cesses 174
 in cirrhosis 231
 concentration of in hepatic
 lymph 151
 effect of radiation on 656
 in mitochondria 21
 in nuclei 22
 in regeneration of liver 92
 relation of to metabolic pool
 25-26
 Lipogenic 38
 Lipofuscin 19 20
 in hepatic cell 19
 in Kupfer cells 19
 location of 19
 occurrence of 19
 PAS action of 19
 in vesicles 19
 Lipogenesis 28
 Lipogenic factor 496-497
 Lipogenic lipotropic substratum
 496-499
 functional manifestations of
 497-498
 pathogenesis of 496-497
 lipogenic factor in 496-497
 lipotropic factors in 497
 structural change in 496-499
 cero 498-499
 Lipocyte acid 25 56
 Lipolytic theory of Vizzini 33
 Lipom 616
 Lipoproteins 12 316 319 733
 Lipotropic pancreatic 38
 Lipotropic activity of vitamin
 B₁ 33 53
 Lipotropic agents 5-53
 in cirrhosis 514
 Lipotropic amino acid 39
 Lipotropic deficiency hemolysis
 renal changes in 648
 Lipotropic factors 497
 in crude liver extracts 33
 Lipotropic methyl donors 33
 Lipotropic 32 37-39
 present concept of objections
 to 33-39
 Liver and cardiovascular system
 651
 and central nervous system
 652-653
 effect of on hematopoietic sys-
 tem 627-629
 endocrine pancreas 632-634
 fluid depot 651
 and gastrointestinal tract 630-
 632
 gross anatomy of 160-163
 and hematopoietic system par-
 allel involvement of 629
 relation between 624-627
 inflammation of on brain 652-653
 on corpus luteum hormones
 645
 on kidney 648
 on pancreas 632-633
 on spleen 623
 on testosterone metabolism
 645
 inflammation of on brain 653
 of hematologic disorders 629
 of kidney 650-651
 of sex hormones 645-648
 of spleen 623
 ligaments of 160
 lobes and surfaces of 160
 nonepithelial tumors of 616
 and normal thyroid gland 483-
 484
 in pancreatic diabetes 633
 and pancreatic islands 639-643
 percussion of 160
 projections of 160
 relation of to endocrine glands
 635-646
 to spleen and hematopoietic
 system 623-629
 and sex organs 643-646
 shape of 160
 and skeletal system 651-652
 topographical anatomy of 160
 161
 weight of effect of meals on
 392
 Liver abscess (see Abscess)
 Liver biopsy (see Biopsy)
 Liver cell cytoplasm 12
 Liver disease diagnosis of prin-
 ciple of 661-669
 lipid and acid synthesis 369
 Live fat in starvation 3-
 (See also Fat)
 Liver flukes 572-573
 Liver function tests 313
 Liver function tests 313
 conditioned 313-314
 true 313
 Liver lobule 157-160
 classic unit of 158-159
 portal unit of 157 158
 percentage of 158
 radius of 159
 shape of 159-160
 (See also Lobules)
 Liver palms 645
 Liver profile 313
 Liver resections hepatic for removal
 of primary or secondary neo-
 plasms 739
 Lobes and surfaces of liver 160
 Lobules ghost 211 258 447
 groups of necrosis of regenerate
 tissue after 92
 intrinsic intralobular regeneration
 in 90
 in (see Liver lobule)
 partial liver destroyed regenera-
 tion and replacement of 90
 92
 subdivision of 289
 Lupus erythematosus 583
 Lupus erythematosus reactions in
 postnecrotic cirrhosis 739
 Lymph (see Hepatic lymph)
 Lymph drainage of liver 150
 Lymph nodes 629
 Lymph spruce 149
 Lymphangectasia 24-
 Lymphangomas 616
 Lymphangitis exudate 24-
 proliferative 242
 Lymphatic changes in ascites 295
 Lymphatic obstruction peritoneal
 cyst 295
 Lymphatic vessel intrahepatic
 149-150
 cystic 150
 gallbladder 150
 periductal 150
 portal 150
 and tissue spaces 149-151
 function of 150-151
 structure of 149-150
 Lymphocytes 629
 Lymphocyte and histiocyte cell
 accumulation of 154
 Lymphoid elements effect of
 hematopoietic system on 629
 Lymphomas 241 624-625
 benign hepatic 245
 Lymphoma 625
 Lysine 28 29 495
 M
 Ma Mahon 545
 McNaughton's classification of jaundice
 180
 Magad 218
 Magnesum 6-
 in bile 81
 in cytoplasm 12
 magnesium chloride-flocculation
 test 339
 Magnesum ions 25
 Magnesum levels 23
 Malna extrahepatic phase of
 459

- Malarial hepatitis 458-459
 laboratory findings in pertaining to liver, 458
 structural alterations in extensive hepatic necrosis 459
 extravascular phase of malaria 459
 malarial cirrhosis 459
 Maltese 25
 Malformations of biliary system 170-172
 of gallbladder 173
 of liver 169-170
 abnormal lobulation 169
 clinical significance of 169
 hypoplasia of lobes 170
 complete absence of liver 170
 in situs inversus 170
 indentations 170
 congenital diaphragmatic herniation 170
 eventration of right diaphragm 170
 costal arch grooves 170
 rib impressions 170
 sagittal furrows 170
 polyps 169-170
 Mall 1-7
 space of 149
 Mallory F B 26
 Mallory bodies 203-238
 Mallory's aniline blue stain 10
 Malnutrition as cause of edema 240
 fatty liver cirrhosis syndrome from 504-519
 iron pigment in 101
 malignant (see Tropical malnutrition)
 modifying clinical course of hepatitis 424
 in parallel involvement of pancreas and liver 633-634
 tropical (see Tropical malnutrition)
 Malpositions of gallbladder 173
 of liver 169-170
 clinical significance of 169
 Manganese 62 396 401
 Manganese dioxide in phagocytosis 98
 Manganous chloride 196
 Mann 218
 Masson's trichrome stain 10
 Mechohy 147
 Megaloblastic maturation arrest 623
 Melanoblastomas primary 616
 Melasiderosis 199
 Melena associated with carcinoma of papilla of Vater 189
 rupture of varix as cause of 290
 Meltzer's law 117 119
 Membrane formation central 259 261
 periportal 261
 Membranes 255
 intralobular formation of 259
 Menstrual irregularities 644
 Menstruation influencing results of tests 662
 Menthol 69
 Mercaptane acid 68
 bromobenzene excreted as 69
 Mercunol diuretics as therapy for ascites 96
 Mercuric chloride-titration test 330
 Mesenchymal cells 97-98
 Mesenchymal elements in formation of epithelial hepatic cell plates 163
 Mesobilifuscin 73 78
 Mesobilirubin 72 78
 Mesobilirubinogen 72 78
 Mesoporphyrin 79
 Metabolic function of Kupffer cells 100-101
 Metabolic hepatic injury 532-547
 classification of 532
 Metabolic pathway of estrogen in activation 643-644
 Metabolic pathways common 27
 Metabolic pool 24-25
 acetate in 25
 formate in 25
 pyruvate in 25
 relation of carbohydrates to 25
 relation of lipids to 25-26
 relation of proteins to 26
 Metals 400-401
 Metastases detection of in proved carcinoma 619
 Methemalbumin 74
 Methemoglobin 72
 Methene bridges 71
 Methimazole 402
 Methionine 26 27 29 38 218
 252 738
 administration of 500
 in fatty cirrhosis 39
 effect of on phospholipid turnover 34
 oral neurologic symptoms following 735
 urinary excretion of 45
 Methionine deficiency 495
 Methionine tolerance tests 339
 Methyl chloride 400
 Methyl donors 27
 lipotropic 38
 Methyl green pyronin stains 12
 Methyl groups 37
 as essential dietary constituents 38
 Methyl radical 27
 Methylation 38
 Methylene blue for determination of bilirubin in urine 352
 Methylmercaptan 221 735
 Methyltestosterone 196 229
 Methyltestosterone, pseudice 403-404
 Meyenberg complexes 170 587
 553 739
 Microcilia 184 229 232
 Microhamartomas 739
 multiple 587
 Microles 232
 Microscopic study 9-12
 Microscope electron 12
 fluorescence 12
 phase 12
 supravital 11-12
 ultraviolet 12
 Microsomal fraction 734
 Milk of calcium bile 116 301
 Millon reaction 218
 Millon test for demonstration of tyrosine in urine results of 338
 technique for 338
 tyrosinase method 338
 Minerals 217 219
 tests concerning 366-367
 Mitochondria 12 20-21 25 27 67
 and bile secretion 84
 Mitosis 87
 stimuli for 111
 Mongolism fatty liver in 253
 Monocytes 101
 wandering 154
 Mononucleosis infectious hepatitis caused by 454-455
 clinical hepatic manifestations in 454
 incidence of hepatitis involvement in 454
 laboratory findings in 454-455
 hematologic differential diagnosis from viral hepatitis 454
 hepatic tests 454-455
 structural hepatic alterations in 455
 Moon 262
 Morphine 68
 Mucin in bile 81
 Mucoproteins 216 28
 in bile 81
 Mucosal block against iron absorption 61
 Mucoviscidosis 171
 Multinucleated cells in regeneration 90
 Mushroom poisonous 400
 Mushroom intoxication 411
 Myeloid/erythroid ratio 128
 Myeloid metaplasia agnogenic 565
 idiopathic 624
 Myeloma 625
 multiple 625
 Myeloproliferative disorders 624
 Myocarditis and electrocardiographic changes 737
 N
 Naphthalene 67
 chlorinated 396 400
 Naphthol 83
 Necrosis in liver disease 69
 Nanny 179 184
 Necropsy specimens of postnecrotic cirrhosis 450-451
 Necrosis 205-214
 acute as sequela of fatty metamorphosis 254
 anoxic 143 213
 crystalline 552
 central in acute reduction of hepatic vein flow 208
 during agonal period 174-175

- Necrosis central without associated focal necrosis 227
in autopsy specimens 205
in bromobenzene intoxications 205
in carbon tetrachloride intoxications 204
etiology of 203
experimental 203
without fat 396
with fatty metamorphosis 393-396
in hepatic artery ligation 203
histologic alterations in autopsy specimens 405-411
histologic findings of 203
in low atmospheric pressure 203
microscopic appearance of 203
in portal congestion 203
in perfusion of liver with peripheral venous blood 203
in shock 203
toxic vs congestive 203
functional impairment in 203
- dietary 499-500
fatty liver without 398
following fatty degeneration 227
focal 203, 207, 241-245, 398
cellular response to 207
hepatic (see Hepatic necrosis)
hepatic cell in cholestasis 227-229
and hepatocellular degeneration (see Hepatocellular degeneration, and necrosis)
of isolated hepatocellular cells 27
massive 211-213, 434-438
changes in other organs 436
brain 439
gastrointestinal tract 438
kidneys 438
lymphoid hyperplasia 436
meningoencephalitis 438
spleen 436
testes 439
collapse of entire lobules 434
in weight 436
etiology of 213
histologic alterations of 434-438
acute nonfulminant form 436
fulminant form 434-438
macroscopic appearance of 434
morphogenesis of 436
molecular 211
alteration in chloroform to hypertrophic degeneration 211
in burn 211
histologic alterations in autopsy specimens 211
in portal congestion 211
after trauma 211
in yellow fever 211
miliary 552
- Necrosis in nonjaundiced animals
etc rats with one common duct ligated 227
pancreatic in viral and toxic hepatitis 633
peritoneal 211, 396, 736
in allyl formate intoxication 211
in chloroform intoxication 211
in cirrhosis 211
in eclampsia 211
in extrahepatic cholestasis 211
in furoic sulfate poisoning 211
histologic alteration in autopsy specimens 411
injection of oil into branches of hepatic artery and portal vein 211
in phosphorus intoxication 211
in viral hepatitis 211
peritoneal 232
reticular 232
reticular biliary 227
postradial hepatitis with (see Viral hepatitis with post-radial necrosis)
subacute massive morphogenesis of 449
submucosa 211-213
etiology of 212-213
toxic hepatic (see Toxic hepatic necrosis)
zonal 203
- Necrotic liver tissue effect of 652
- Nematode 372
- Neoplasms experimental hepatic
cells of types of 595-598
definition of 595-597
histology of 595-597
bile ductal and ductular nodule 597
hepatic carcinoma from butter yellow 597
hepatocellular nodule 597
- Nephrosis acute 649
acute segmental 649
biliary 648-649
cholemic 649
glomerulular 649
lower nephron 649
necrotic 649
neurosis 440-441
- Neroma formation 309
- Neuropsychiatric complications of liver disease 852
- Nutritional 18, 25, 32-33
amount of 32
in bile 33
in serum 33
- Neutropenia 628
- Nicotinic 57
vasodilating effect of on liver 57
- Niacin deficiency 57
- Niacinamide 23
- Nicotinamide 28
- Nicotine 63
- Niemann-Pick disease 545
- Nitrogen 41
nonprotein (see NPN)
Nitrogen metabolism in tests concerning 333-339
Nitrogen mustard 396
Nocua distans 567
- Nodules 735
bile ductal and ductular in experimental hepatic neoplasms 597
hepatocellular in experimental hepatic neoplasms 597
histiocytic or reticuloendothelial 552
hyperplastic 92
regenerating compression of hepatic vein branches by 254
regenerative 92, 262
carcinoma 512
formation of 22, 274
- Nonportal zones in rat livers 149
- Norepinephrine 639
- NPN (nonprotein nitrogen) 217
in bile 81
and urea determination of 335-339
evaluation of 339
physiologic basis of 335-339
results of 339
- Nuclear elements in liver 44
nuclear chromatin 16
nuclear glycogen and congestive heart failure 22
and diabetes mellitus 22
- Nuclear inclusions 23
- Nuclear maturation factor 627-628
- Nuclear pentose nucleic acids 8
- Nuclear variations binucleated cells 23
dark cells 23
hyperchromatic nuclei 23
nuclear acid stains 11
- Nucleic acids 16
- Nucleolus 16, 22
function of 22
and protein deficient diets 23
and protein in regrowth 23
size of 23
and starvation 23
- Nucleolus associated chromatin 22
- Nucleoprotein and vitamin B₁ 57
- Nucleoprotein catabolism 45
- Nucleus 21-23, 87
of hepatic cells 21
nuclear cytoplasm 34
- Nutritional cirrhosis with fatty metamorphosis 513-516
clinical manifestations of 513
laboratory findings in 513-514
nomenclature of 513
structural alterations in 514
histologic changes 514
macroscopic appearance 514
therapeutic aspects of 514
chloroform administration 514
intravenous administration of human serum albumin 516

- Nutritional cirrhosis with fatty metamorphosis therapeutic aspects of hypotrophic agents 514
 testosterone 516
 Nutritional deficiencies 493-496
 deficiency of specific amino acids 495-496
 cystine deficiency 496
 ethionine administration 495
 methionine deficiency 495
 deficiency of total protein 493
 495
 types of protein deficiency 493
 various excesses and deficiencies 496
 Nutritional factors modification of intoxications by 500-501
 interrelation of beneficial effects in 501
 Nutritional fatty liver with hepatic cellular degeneration 507-510
 clinical manifestations of 507
 laboratory findings in 507
 structural alterations in 507-510
 biopsy specimens 508-510
 histologic changes 507-509
 macroscopic appearance 507
 therapeutic considerations in 510
 Nutritional hepatic injury 492-502
 in animals 493-496
 classification of 503
 clinical entities in 503-510
 from dietary imbalance 496-501
 effects of alcohol on liver 501-502
 Nutritional siderosis 534-535
- O
- Obesity fatty liver in 503
 Oleic acid and bile flow 83
 Omentopexy 291
 Omphaloenteric veins 185
 186
Opisthorchis felinus 573
 Ornithine 27
 Osmotic pressure of hepatic cell in carbon tetrachloride 62
 in low protein diets 62
 in obstruction of common bile duct 62
 Osteomalacia 652
 Osteoporosis 237
 Ovalacetrin 25
 Oxidation 67
 Oxidative enzyme activity 213
 Oxygen amount of provided to liver by hepatic artery and portal vein 139
 Oxygen saturation in hepatic vein 145
- P
- pH of bile 80
 of liver 62
 in hepatomas 62
 Pinn biliary tract 153-154
 hepatic 153
 Palmar erythema 739

- Palmar erythema in clinical hyperestrogenism 645
 Pancreas carcinoma of 633
 exocrine and liver relation between 633-634
 fibrocystic disease of postneurotic cirrhosis in 739
 inflammatory or cystic lesions in 191
 influence of on liver 633
 experimental studies in 633
 influence of liver on 632-633
 and liver parallel involvement of 633-634
 alcoholism 633
 hepatic disease 633
 malnutrition 633-634
 pathogenesis of 634
 in liver disease 632-633
 Pancreatic disease liver in 633
 pancreatic duct and bile duct relationship 632
 Pancreatic fibrosis 632
 Pancreatic islands and liver relation between 639-643
 Pancreatic juice 307
 bilirubin in 198
 Pancreatic lipotropes 38
 Pancreaticohepatic syndrome 633
 Pancreatitis acute 633
 biliary 633
 chronic relapsing 633
 jaundice in 633
 postoperative 309
 transient postoperative after biliary tract surgery 191
 Panmyelopoiesis 585
 Panmyelosis 624
 Pantothenic acid 25 57
 Pantothenic acid deficiency relation of to fatty livers 57
 Papilla of Vater 107 108 632
 common channel at 109
 inflammation of 248
 innervation of 153
 Papilloma benign of ampulla 59
 of gallbladder 592
 Para aminobenzoic acid 67 68
 Para aminobenzyl caffeine hydrochloride 737
 Para aminoluppurate synthesis 369
 Para aminohippuric acid 67
 Para aminosalicylic acid (see PAS)
 Para amyloid 557
 Paracentesis as therapy for ascites 296
 untoward effects of 296
 Parachole 179
 Paracresol 68
 Paraffin 10
 Parasites in bile ducts 193
 in Kupffer cells 98
 Parasitic diseases of liver 569-578
 Paratyphoid fever 564
 Pirrumbilical veins anomalous dilatation of 131
 of Sappey 131 133
 Pirene lymphomatous degeneration 202
 Partition theory of Frazer 33
 PAS (para aminosalicylic acid) 67 196

- PAS stains for amebas 11
 for fungi 11
 for interlobular bile ducts 11
 for reticulum framework 11
 for wear and tear pigments 11
 PAS treatment jaundice following 404
 Patton tube 291
 Pavel theory of on jaundice 180-181
 Pectoral alopecia 644
 Peliosis 555 583
 Pellagra tropical (see Tropical malnutrition)
 Penicillamine 217
 Penicillin 402
 Penicillin treatment following ligation of hepatic artery 143
Pentastemon denticulatus 578
 Pentidoponts 73 75 78
 Pentose 25, 30
 Pentose nucleic acid (see PNA)
 Pentose nucleic acid protein (see PNA granules)
 Pentose nucleoproteins of cytoplasm 18 18
 Peptic ulcer 631
 bleeding from in cirrhosis 290
 and cirrhosis coexistence of 630
 Peptic ulceration 290
 Peptides urinary excretion of 44
 Peptiduria 542
 Peptone 147
 Percussion of liver 180
 Periarthritis nodosa 633
 Peribiliary plexus 136
 Pericholangiolitis 242
 and cholangiolitis 462-467
 Pericytes 94
 Periductal lymphatic vessels 150
 Perihepatitis 480-481
 Perilobular ductules 106
 Perilymphangitis 242
 Perisinusoidal spaces of Disse 94
 Pentoneoscopic biopsy 379-380
 Pentoneoscopy 620
 Personality changes 223
 Pettenkofer reaction for determination of bile acids in urine 365
 for determination of serum bile acids 365
 Pfuhl 135
 Phagocytic activity of Kupffer cells 12
 Phagocytosis bacterial 98 99
 during blockade 101
 of blood cell 99
 of colloidal material by Kupffer cells 734
 of eosinophils 99
 general factors in 98
 mechanism of 98
 bile acids in 98
 detergents in 98
 vital microscopic investigations in 98
 Phase microscopy for visualization of changes of mitochondria 12
 Phenobarbital 402
 Phenolphthalein 66

- Necrosis central without associated focal necrosis 227
 in autopsy specimens 208
 in bromobenzene intoxications 208
 in carbon tetrachloride intoxications 208
 etiology of 208
 experimentally 208
 without fat 396
 with fatty metamorphosis 393-396
 in hepatic artery ligation 209
 histologic alteration in autopsy specimens 408-411
 histologic findings of 209
 in low atmospheric pressure 208
 macroscopic appearance of 208
 in passive congestion 208
 in perfusion of liver with peripheral venous blood 208
 in shock 208
 toxic vs congestive 208
 functional impairment in 208
- decreased 499-500
 fatty liver without 398
 following feathery degeneration 227
 focal 205 207 241-245 396
 cellular response to 207
 hepatic (see Hepatic necrosis)
 hepatocellular in cirrhosis 227-228
 and hepatocellular degeneration (see Hepatocellular degeneration, and necrosis)
 isolated hepatic cells 227
 massive 211-213 434-439
 changes in other organs 438-439
 brain 438
 gastrointestinal tract 438
 kidneys 438
 lymphoid hyperplasia 438
 meningoencephalitis 438
 spleen 438
 testes 438
 collapse of entire lobules following 226
 etiology of 213
 histologic alterations of 434-438
 acute nonfulminant form 438
 fulminant form 434-438
 macroscopic appearance of 434
 morphogenesis of 436
 malignant 211
 after administration of chloform to hyperthyroid rabbits 211
 in burns 211
 histologic alterations in autopsy specimens 411
 in passive congestion 211
 after trauma 211
 in yellow fever 211
 biliary 552
- Necrosis in nonjudiced parabiotic rats with one common duct ligated 227
 pancreatic in viral and toxic hepatitis 633
 peripheral 211 306 736
 in allyl formate intoxication 211
 in chloroform intoxication 211
 in cirrhosis 211
 in eclampsia 211
 in extrahepatic cholestasis 211
 in ferrous sulfate poisoning 211
 histologic alteration in autopsy specimens 411
 by injection of oil into branches of hepatic artery and portal vein 211
 in phosphorus intoxication 211
 in viral hepatitis 211
 perportal 232
 reticular 232
 reticular biliary 227
 spotty viral hepatitis with (see Viral hepatitis with spotty necrosis)
 subacute massive morphogenesis of 449
 submassive 211-213
 etiology of 212-213
 toxic hepatic (see Toxic hepatic necrosis)
 zonal 208
- Necrotic liver tissue effect of 655
- Neomorphosis 572
 Neoplasms epimeral hepatitis
 cell of types of 513-596
 definition of 596-597
 histology of 59-597
 bile ductal and ductular nodular 597
 hepatic carcinoma from butter yellow 597
 hepatocellular nodular 597
- Nephrosis acute 649
 acute segmental 649
 biliary 649-649
 cholemic 649
 glomerulotubular 649
 glomerular 649
 necrotizing 649
- Neurasthenia and dyspepsia 440-441
- Nephroma formation 309
- Neuropsychiatric complications of 1 disease 652
- Neutrophils 18 25 3-33
 amount of 32
 bile 33
 in serum 33
 neutrophils 628
 Neutrophils 57
 vasodilating effect of on liver 57
- Niacin deficiency 57
 Nicotinic acid 253
 Nicotinic acid 38
 Nicotine 68
- Niemann Pick disease 545
- Nitrogen 41
 nonprotein (see NPN)
 nitrogen metabolism tests concerning 333-339
 nitrogen mustard 336
 Nocardia asteroides 587
- Nodules 735
 bile ductal and ductular in experimental hepatic neoplasms 597
 hepatocellular in experimental hepatic neoplasms 597
 histiocytic or reticuloendothelial 552
 hyperplastic 92
 regenerating compression of hepatic vein branches by 284
 regenerative 92 282
 carcinoma 55 612
 formation of 272-274
- Nodular zones in rat livers 149
 epinephrine 635
- NPN (nonprotein nitrogen) 217 218
 in bile 81
 and urea determination of 339-339
 measurement of 339
 physiologic basis of 339-339
 results of 339
- NPN levels in liver 44
- Nuclear chromatin 18
- Nuclear glycogen and congestion
 heart failure 22
 and diabetes mellitus 22
- Nuclear inclusions 23
- Nuclear maturation factor 627-629
- Nuclear peptide nucleic acids 87
- Nuclear variations binucleated cell 23
 "dark cells" 23
 type chromatin nuclei 23
- Nucleic acid stains 11
- Nucleic acids 18
- Nucleolus 18 22
 function of 22
 and protein-deficient diets 23
 and protein depletion 23
 size of 23
 and starvation 23
- Nucleolus associated chromatin 22
- Nucleoprotein and vitamin B₁ 57
- Nucleoprotein catabolism 45
- Nucleus 21-23 87
 of hepatocellular cells 21
- Nucleus cytoplasm 34
- Nutrition 1 curthous with fatty metamorphosis 513-516
 clinical manifestations of 513
 laboratory findings in 513-514
 nonenrichment of 513
 structural alterations in 514
 histology changes 514
 macroscopic appearance 514
 therapeutic aspects of 514
 choline administration 514
 intravenous administration of human serum albumin 516

- Nutritional cirrhosis with fatty metamorphosis therapeutic aspects of lipotropic agents 514
testosterone 516
- Nutritional deficiencies 493-496
deficiency of specific amino acids 495-496
cystine deficiency 496
ethionine administration 495
methionine deficiency 495
deficiency of total protein 493-495
types of protein deficiency 493
various excesses and deficiencies 496
- Nutritional factors modification of intoxications by 500-501
interrelation of beneficial effects in 501
- Nutritional fatty liver with hepatocellular degeneration 507-510
clinical manifestations of 507
laboratory findings in 507
structural alterations in 507-510
biopsy specimens 509-510
histologic changes 507-509
macroscopic appearance 507
therapeutic considerations in 510
- Nutritional hepatic injury 492-502
in animals 493-496
classification of 503
clinical entities in 503-510
from dietary imbalance 496-501
effects of alcohol on liver 501-502
- Nutritional siderosis 534-535
- O
- Obesity fatty liver in 503
- Oleic acid and bile flow 83
- Omentopexy 291
- Omphalomesenteric veins 165, 166
- Opisthorchis felinus 573
- Ornithine 27
- Osmotic pressure of hepatic cell in carbon tetrachloride 62
in low protein diets 62
in obstruction of common bile duct 62
- Osteomalacia 652
- Osteoporosis 237
- Oxalacetate 25
- Oxidation 67
- Oxidative enzyme activity 233
- Oxygen amount of provided to liver by hepatic artery and portal vein 139
- Oxygen saturation in hepatic vein 145
- P
- pH of bile 80
of liver 62
in hepatomas 62
- Pain biliary tract 153-154
hepatic 153
- Palmar erythema 739
- Palmar erythema in clinical hyperestrogenism 645
- Pancreas carcinoma of 633
endocrine and liver relation between 632-634
fibrocytic disease of postneoplastic cirrhosis in 739
inflammatory or cystic lesions in 191
influence of on liver 633
experimental studies in 633
influence of liver on 632-633
and liver parallel involvement of 633-634
alcoholism 633
hepatic disease 633
malnutrition 633-634
pathogenesis of 634
in liver disease 632-633
- Pancreatic disease liver in 633
- Pancreatic duct and bile duct relationship 632
- Pancreatic fibrosis 632
- Pancreatic islands and liver relation between 639-643
- Pancreatic juice 307
- Bilirubin in 199
- Pancreatic lipotropes 38
- Pancreatohepatic syndrome 633
- Pancreatitis acute 633
biliary 633
chronic relapsing 633
jaundice in 633
postoperative 309
transient postoperative after biliary tract surgery 191
- Panmyelopoiesis 585
- Panmyelosis 624
- Pantothenic acid 25, 57
- Pantothenic acid deficiency relation of to fatty livers 57
- Papilla of Vater 107, 108, 632
common channel at 108
inflammation of 143
innervation of 153
- Papillomas benign of ampulla 592
of gallbladder 592
- Para aminobenzoic acid 67, 69
- Para aminobenzyl caffeine hydrochloride 737
- Para aminohippuric acid 67
- Para aminosalicylic acid (see PAS)
- Para amyloid 557
- Paracetamol therapy for ascites 296
untoward effects of 296
- Parachol 179
- Paracetamol 69
- Paraffin 10
- Parasites in bile ducts 193
in Kupffer cells 96
- Parasitic diseases of liver 569-578
- Paratyphoid fever 584
- Parumbilical veins anomalous dilatation of 131
of Sappey 131, 133
- Parenchymatous degeneration 202
- Partition theory of Fraser 33
- PAS (para aminosalicylic acid) 67, 196
- PAS stains for amebas 11
for fungi 11
for interlobular bile ducts 11
for reticulum framework 11
for wear and tear pigments 11
- PAS treatment jaundice following 404
- Patton tube 291
- Pavlov theory of on jaundice 180-181
- Pectoral alopecia 644
- Peliosis 555, 583
- Pellagra tropical (see Tropical malnutrition)
- Penicillamine 217
- Penicillin 402
- Penicillin treatment following ligation of hepatic artery 143
- Pentastomum denticalum 578
- Pentidypents 73, 75, 78
- Pentose 25, 38
- Pentose nucleic acid (see PNA)
- Pentose nucleic acid protein (see PNA granules)
- Pentose nucleoproteins of cytoplasm 16, 18
- Peptic ulcer 631
bleeding from in cirrhosis 290
and cirrhosis coexistence of 630
- Peptic ulceration 290
- Peptides urinary excretion of 45
- Peptiduria 542
- Peptone 147
- Perfusion of liver 160
- Periarthritis nodosa 633
- Peribiliary plexus 136
- Pericholangiolitis 242
and cholangiolitis 462-467
- Perineves 94
- Penductal lymphatic vessels 150
- Perihepatitis 480-481
- Peribiliary ductules 106
- Perihepatitis 242
- Perinodular spaces of Disse 96
- Pentoneoscopic biopsy 379-380
- Pentoneoscopy 620
- Personality changes 223
- Pettenkofer reaction for determination of bile acids in urine 365
for determination of serum bile acids 365
- Pfuhl 135
- Phagocytic activity of Kupffer cells 12
- Phagocytosis bacterial 98, 99
during blockade 101
of blood cells 99
of colloidal material by Kupffer cells 774
of eosinophils 99
general factors in 93
mechanism of 93
bile acids in 98
detergents in 98
vital microscopic investigations in 98
- Phase microscopy for visualization of changes of mitochondrial 12
- Phenobarbital 402
- Phenolphthalein 86

- Placenta 68
 excret on of as etil ereal sulf tes 68
 as gl curonates 68
 Phenolst ilionphthal in (PSP) he
 patie e cretion of 85
 Phenurone 40
 Phenylacetic acid 67
 Phenyl lamine 26 28
 Pl enilbuta one 737
 Phenylid chloro rs ne 396
 Pl ehosclerosis 579 583
 Phlegmonous inbiration 303
 Phl h in intor cat d animal 28
 Pl k vine methyl ne blue stain 10
 Pl ospil itase 30
 in bile 81
 hepatic 47 213
 in nuclei 22 47
 Pl ophate bond l gh e e sy 25
 Pl sphates in bile 81
 Pl ophogalacto omerase 31
 Phosphogluc n itase 30
 Phosphogluc n c ad 25
 Phospholipid synth s 34
 Pl ospil pid turnover reduced
 after chol sterol feeding 36
 Pho pholipids 25 33-34 213
 in bile 81
 and cholesterol sol t n be
 tween 36
 composition of 33
 in cytoplasm 12
 funct on of 33
 in hepatectomized animals 34
 in h p tic format on of 34
 in h pat e disease 34
 hepatic uptake of 34
 intestinal abso ption of 33 34
 in m tochondria 21
 renewal of rate of 34
 serum (see Serum phospho
 lipids)
 turnover of 34
 Phosph pyndine nucleotides 45
 Pho phorus 59 394 400
 eff ct of irradi at on on 657
 radioact e 655
 incorporated n nucle e PNA
 fraction 3
 Ph sphorus poison 18 411
 Phospho lyas e 30
 Phosphorylat on 30
 Photogr ply infra d 131 13
 91
 Plure c ner e 153
 Phrygan eip 110 115 173
 Pl the plate ydium 402
 Physiolog c det ry variat ons in
 fluence of 49 -493
 d rnal variat ns 49
 effect on h patie tests 493
 P ks p eud r rhosis 451
 Picric acid 199
 Pig m t granu l g
 Pigment m t l oisim 70-79
 Pl ocarp ne 147 298
 Press n 636
 P tuary anhd etic horm ne
 294 295
 P tuary extracts anterior 30 635
 P tuary gland 635-636
 Pituitary growth hormone 32

- Portal vein complete ligation of
in man 141
congenital anomalies of 286
congenital strictures of 286
constriction of simultaneously
with ligation of abdominal
portion of inferior vena
cava 286
diseases of 579-581
extrahepatic portion of 127
function of 139
gradual compression of 141-
142
in animals 141
in man 141-142
internal radicles of 125 130
136
intrahepatic portion of 127 130
interlobular veins 127
venous drainage of peribiliary
plexus 130
venules 130
length of 127
and liver effect of portal hyper-
tension on 287
obliteration of 286
occlusion of 8
radicular 125 130
rate of flow in 141
relation of to hepatic artery
blood flow 139
streamlines of flow of 139-140
Portal vein branches and hepatic
vein branches anastomoses
between 136
Portal vein compression 286
Portal vein-hepatic artery anasto-
moses 136
Portal vein obstruction 131
sudden in animals 141
in man 141
Portal vein oxygen saturation 140-
141
Portal vein pressure 140
Portal vein thrombosis (see
Thrombosis portal vein)
Portocaval gradient 140
Portocaval shunt 93 291
Portosystemic anastomoses 130-
133 277
abnormal 167
anomalies 130-131
esophageal and diaphragmatic
veins 133
hemorrhoidal veins 133
normal communications 131
retroperitoneal veins 133
umbilical vein and paraumbilical
veins of Sappey 131 133
Portosystemic encephalopathy
223
Postcholecystectomy syndrome
308-309
Postcollapse 286
Posterior pituitary hormones 636
Postmortal and agonal changes
(see Agonal and postmortal
changes)
Postnatal development 169
Potassium 58-59
in anoxia 59
content of in liver 58
in cytoplasm 12
Potassium determination of 367
and epinephrine 59
in hepatic disorders 59
and insulin 59
Potassium ions 30
Pr coma hepatic 219
ammonia administration or
high protein diet inducing
224
triad of 224
Pregnancy and cholelithiasis 301
hepatic changes in 486 488
influencing results of tests 662
modifying clinical course of
hepatitis 424
rupture of liver during 654
Pressure intrahepatic 283
intrasplenic 283
portal epinephrine increasing
286
food intake producing tem-
porary rise in 286
histamine increasing 286
measurement of 283-284
wedge 283 236
Primary hepatic carcinoma 593-
612 739
age and sex incidence of 60
in childhood and infancy 610-
612
clinical differential diagnosis of
61
clinical manifestations of 603-
604
environmental factors in 602
geographic distribution of 60
grading of 609
histogenesis of 599-601
human 599-612
incidence of 602
laboratory findings in 604
nomenclature of 601
racial factors in 602
relation of to cirrhosis 602-
603
structural alterations in 604 609
histologic changes 604 609
variations in 604 609
macroscopic appearance 604
structural differential diagnosis
of 612
gross features in 612
microscopic features in 612
therapy for 612
uncentric or multicentric origin
of 601
unusual types of 610
carcinoma in hemochromato-
sis 610
cercariosis 610
mixed hepatobiliary carci-
noma 610
(See also Tumors)
Prodax 374
Progesterone 67
Projections of liver 160
Proliferated ductiles origin of
120
Proliferation ductular 119-120
causes of 120
forming gross nodules in retic-
ulum cell sarcoma 101
in Hodgkin's disease 101
Proliferation in intralobular ty-
phoid nodule 101
of Kupffer cells and portal lym-
phocytes 41
in non lipid storing reticuloen-
dotheliosis of Letterer-Siwe
type 101
and regeneration 101
Proline 28
Propenylpivopents 73
Propylthiouracil 402
Prostate gland changes in
clinical hyperestrogenism 644
Protein binding of cholesterol 36
Protein catabolism tests related
to 337-339
Protein concentration in cirrhosis
151
of hepatic lymph 151
in passive congestion 151
Protein content of ascitic fluid
293
Protein deficiency types of 493
Protein deficient diets enzymes
in 46
and nucleolus 23
Protein depletion 41
Protein formation 40 41
hepatic 41
rate of 41
site of 16
Protein hydrolyzates 296
Protein intake excess 496
Protein metabolism 40
effect of insulin on 639-640
and mitochondria 21
and nitrogen metabolism 216
217
tests concerning 333-339
Protein reactions non specific fac-
tors influencing results of
323-324
Protein solutions separation of
methods of 317
Protein synthesis 27 40 45 87
Proteins 299
bile 81
and bile flow 83
Cerebrine 282 334
catabolism of 44-45
concentration of 41
of cytoplasm 12 15-16
half life of 41
in hepatectomized animals 41
in hepatic lymph 151
as lipotropic methyl donors 38
plasma (see Plasma proteins)
in regenerating liver 92
and regeneration 92
relation of to metabolic pool
26-27
serum (see Serum proteins)
stricture of 44
total deficiency of 493 495
types of 41
Proteolysis 44 273
Proteolytic enzymes 28 50
Prothrombin 43 219 237 334
composition of 43
molecular weight of 43
relation of to vitamin K 43
slow fall in congenital atresia
of bile ducts 220

- Rift Valley fever hepatitis 456
 Rocky Mountain spotted fever 407
 Roentgenologic Courvoisier sign 375
 Roentgenologic visualization of liver and biliary tract 371-378
 Rokutansky 411
 Rose bengal 85 86
 radioactive 86
 Rose bengal test 373
 Rossie 62
 Roundworms 572
 Rupture of liver intraportum 654
 mortality in 654
- S
- Sacculae 106 113
 Salicylates 31 83
 excretion of as glucuronates 68
 Salicylic acid 67
 Saliva in ascites 294
 bilirubin in 198
 Salmonella hepatitis 407
 Salmonella infections 241
 Salt depletion syndrome 298
 Santonin 67
 Santorini duct of 632
 Sarcoidlike lesions, berylliosis 559
 eosinophilic infiltrations 559
 erythema nodosum 559
 nonspecific granulomatous hepatitis 559
 Sarcoidosis 556-559
 as hepatic disease 559
 hepatic reaction in 556-557
 histologic differential diagnosis of 559
 incidence of in biopsy specimens 557 558
 laboratory findings in 556-557
 liver biopsy in 557
 structural alterations in 557 559
 life cycle of follicle 557 559
 mature follicle 557
 Sarcoma hemangioendothelial 591
 malignant hemangioendothelial 616
 undifferentiated 616
 Saturation of fatty acids 32
 Scarring in cirrhosis 282-283
 postnecrotic 283
 of Himsworth 266
 Schiff's periodic acid routine (PAS) 11
 Schistosoma 568
 Schistosoma haematobium 573
 Schistosoma japonicum 573
 Schistosoma mansoni 573
 Schistosomal infestations types of 573
 Schistosomiasis 573-575
 clinical manifestations of 573-574
 experimental studies in 573
 laboratory findings in 574
 portal hypertension in 284
 stages of 573
 structural alterations in 574-575
 granuloma formation 575
- Schistosomiasis structural alterations in nonspecific reactive hepatitis 575
 pipestem cirrhosis 575
 septal cirrhosis 575
 Schlesinger reaction 73
 Schlesinger test for determination of fecal urobilinogen 363
 Schmidt test for determination of fecal urobilinogen 363
 Schoenheimer Sperry method for determination of serum cholesterol 319
 Sclerosis infantile 518-519
 Screening tests 667
 Secretin 83
 Secretory granules 12 21
 Secretory pressure of liver 113
 Sedation in acute viral hepatitis 426
 Sedimentation rate in acute viral hepatitis 4-5
 Segments of liver 162 163
 Selenium 398 593
 Senecio, 396 400 516 519 593
 Sengstaken tube 291
 Septal bile ducts 103
 Septum formation central in chronic passive congestion 269
 in repeated toxic injuries 269
 in fatty metamorphosis 269-70
 mechanism of 266 269
 peripheral 269
 primary 266 269-270 278
 in schistosomiasis 575
 Septums 255 261
 types of transforming fatty liver into cirrhosis 270
 Serine 28
 urinary excretion of 45
 Serous hepatitis 151
 Serum normal color of 199
 of patients with viral hepatitis cytotoxic effects of in tissue cultures 737
 specific gravity of estimation of 315
 Serum albumin 18
 determination of 318-319
 evaluation of 319
 methods of Howe method 318
 immunologic methods 318
 salting-out procedures 318
 specific gravity methods 318
 Wolfson and Cohn method 319
 physiologic basis of 318
 results of 318-319
 reduction of in cirrhosis 291
 Serum albumin level 298 319
 in acute hepatitis 319
 in chronic hepatic diseases 319
 in experimental liver damage 319
 in hepatic disease 319
 in human liver disease 42
 normal 319
 Serum alkaline phosphatase 46-49
- Serum alkaline phosphatase in biliary obstruction 47-48
 in cirrhosis without jaundice 48
 determination of 340-342
 evaluation of 342
 methods of 340
 Bodansky 340
 King and Armstrong 340
 physiologic basis of 340
 results of 340-342
 in carcinoma metastases to liver 342
 in cholestasis 341
 in cirrhosis 341
 in granulomatous processes 341-342
 in healthy children 341
 in hepatic abscesses 342
 in hepatic failure 342
 in hepatitis 341
 in normal persons 341
 in Paget's disease 341
 in primary and secondary biliary tumors 341
 in rickets 341
 in sarcoidosis 342
 in starvation 341
 in tuberculosis 342
 in tumors 342
 elevation of in tumor metastases 193
 excess extrahepatic origin of 48
 hepatic origin of 48
 origin of in hepatobiliary diseases 48
 excretion of 47
 formation of hepatic site of 48-49
 in hepatic damage 48
 in infectious hepatitis 48
 in ligation of hepatic vein 48
 origin of 47
 in primary and metastatic carcinoma of liver 48
 Serum amino acids 337
 Serum ammonia 217
 Serum amylase (see Amylase)
 Serum bile acids determination of methods of 365
 Pettenkofer reaction 365
 results of 365
 Serum bilirubin 219
 determination of 354-357
 bilirubin tolerance test 356
 evaluation of 357
 icterus index 354
 physiologic basis of 354
 qualitative van den Bergh reaction in 356
 serum bilirubin 357
 total based on diazo reaction 355-356
 results of 355-356
 in experimental animals 355-356
 in extrahepatic biliary obstruction 355
 in jaundice 355
 normal values 355
 technique of procedure in 355
 reagents for 355

- Serum bili erdin 357
 S rum changes in hepatic cell
 degeneration 215-217
 bilirubin and bil salts 217
 carbohydrate metabolism 215
 enzymes 217
 fat metabol m 215
 minerals 217
 protein and nitrogen metabo-
 lism 216-217
 Serum chloride 219
 Serum cholestals 217
 Serum cholesterol 36-37
 in biliary obstruction 36
 determination of 349-352
 evaluation of 352
 methods of 349-350
 Lieberman Burchard reac-
 tion 349
 Schoenheimer Sperry
 method 349
 technique in apparatus for
 350
 procedure in 350
 reagents for 349-350
 physiol gic basis of 349
 results of in cholesterol
 esters 351-352
 in total serum cholesterol
 350-351
 in cholestasis 350-351
 in hepatocellular damage
 351
 in nonhepatic disorders
 350
 in normal persons 350
 effect of bile acids on 36
 effect of cholestals on 238
 influence of liver on 36
 sources of 36
 Serum cholestase 217
 S rum citrate determination of
 347
 Serum-circulation rection Welt
 mann 313
 Serum electrolytes and minerals
 determination of 367
 S rum esterase 46 50
 determination of 342-343
 fluorimetric 343
 methods of 342
 technique in 342-343
 procedure 343
 reagents for 342-343
 physiol gic basis of 34
 results of 343
 electrophoretic 50
 detection of in cancer 50
 in clinical hepatic failure 50
 after hepatectomy 50
 in pregnancy 50
 relation of to albumin 50
 to albumin globulin 50
 S rum gamma globulin level in
 in liver disease 100
 Serum gamma globulin formation
 in a liver 41
 Serum gamma globulin level in
 circulation 99
 and cytoplasmic basophilic
 Kupfer cells correlation
 between 100
 S rum gamma globulin level ele-
 vation in cirrhosis 252
 in viral hepatitis 99
 Serum globulin total 321-322
 Serum glutamic-oxalacetic amino-
 transferase 736
 Serum glutamic-oxalacetic trans-
 aminase 50
 S rum histamine levels relation of
 to degree of pruritus 238
 Serum hyaluronidase inhibitor
 217 239
 Serum iron determination of 367
 Serum iron level 217
 in acute hepatitis 61
 in differential diagnosis of jaun-
 dice 736
 relation of liver to 61
 in viral hepatitis 736
 Serum lactate determination of
 347
 Serum lipid fractions ratios of 352
 Serum lipids total determination
 of 347-348
 method of 348
 technique in procedure 348
 in 348
 reagents for 348
 standardization 348
 physiol gic basis of 347
 results of 348
 Serum mucoproteins determina-
 tion of evaluation of 334
 methods of 334
 physiol gic basis of 334
 results of in biliary obstruc-
 tion 334
 in hepatic disorders 334
 normal 334
 in secondary hepatic cal-
 culi 334
 S rum neutral fat determination
 of 348
 Serum phospholipid cholesterol e-
 sterification 238
 Serum phospholipid 34
 amount of 34
 determination of 348-349
 evaluation of 349
 methods of 349
 physiol gic basis of 348
 results of 348-349
 sources of 34
 S um potassium 217
 Serum potassium level 23
 in cirrhosis 59
 in hepatic disorders 59
 Serum protein alterations in cir-
 rhosis 251
 Serum protein fractions 315-322
 Serum protein reactions nonspe-
 cific 323-324
 Serum proteins function of
 316-318
 half-life of 318
 total determination of 315-316
 evaluation of 316
 methods of 315-316
 by electrophoresis 315
 by falling-drop appara-
 tus 315
 by flotation in copper sul-
 fate solution 315
 S rum proteins total determina-
 tion of methods of by
 refractive index 315
 by tyroline method of
 Greenberg 315
 physiol gic basis of 315
 in liver diseases 316
 normal values of 316
 in obstructive jaundice 316
 protein deficiency in 316
 Serum prothrombin conversion ac-
 celerator (see Factor VII)
 Serum pyruvate determination of
 347
 Serum sodium 217-219
 Serum sodium level in cirrhosis
 59
 in hepatic disorders 59
 Serum tripeptidase 50
 Serum vitamin A and hepatic vita-
 min A relation between 55
 Serumumucoids 334
 S r liver disorders excretion of 218
 urinary excretion of in liver
 disease 633-639
 Sex differences in liver 646
 Sex hormones effect of on hepatic
 fat deposition 645-646
 influence of on liver 645-646
 Sex organs and liver relation be-
 tween 643-646
 Sifir 414
 Sheep liver anise obic bacteria in
 99
 Shepherder fluke 572-573
 Sheldon's theory of hemochroma-
 tosis 533-539
 Shock hepatic necrosis from
 452-493
 experimental 483
 function of hepatic changes in
 452-493
 human 493
 Stunts portocaval 93 291
 splenorenal 91
 surgical in portal hypertension
 736
 (See also Venous shunt opera-
 tions)
 Sickle cell anemia 491
 clinical manifestations of 491
 erythrophagocytosis in 99
 structural alterations in 491
 Sickle cell crisis 491
 Siderophilin 59-61
 Siderosis 53-535
 endogenous 534
 exogenous 534-535
 nutritional 534-535
 clinical features of 534
 structural alterations in
 534-535
 peripheral iron or blood ad-
 ministration 534
 pathogenesis of 532-534
 transferrin 532 539
 Silicosis 266
 Silicopneumonitis for demon-
 strating arginine rect column
 fibers 11
 Silicosis syndrome 644
 Sinusoidal blood flow variations
 in throughout lobule 125

Rift Valley fever hepatitis 456
 Rocky Mountain spotted fever 407
 Roentgenologic Courvoisier sign 375
 Roentgenologic visualization of liver and biliary tract 374-378
 Rokitsansky 411
 Rose bengal 85 86
 radioactive 86
 Rose bengal test 373
 Rossle 262
 Roundworms 572
 Rupture of liver intrapartum 654
 mortality in 654

S

Sacculae 106 113
 Salicylates 31 83
 excretion of as glucuronates 68
 Salicylic acid 67
 Saliva in ascites 294
 bilirubin in 195
 Salmonella hepatitis 407
 Salmonella infections 241
 Salt depletion syndrome 296
 Santonin 67
 Santorini duct of 632
 Sarcoidlike lesions berylliosis 559
 eosinophilic infiltrations 559
 erythema nodosum 559
 nonspecific granulomatous hepatitis 559
 Sarcoidosis 558-559
 as hepatic disease 559
 hepatic reaction in 558-559
 histologic differential diagnosis of 559
 incidence of in biopsy specimens 557 558
 laboratory findings in 558-559
 liver biopsy in 557
 structural alterations in 557
 559
 life cycle of follicle 557 559
 mature follicle 557
 Sarcomas hemangioendothelial 591
 malignant hemangioendothelial 616
 undifferentiated 616
 Saturation of fatty acids 32
 Scarring in cirrhosis 282-283
 postnecrotic 263
 of Humsworth 266
 Schiff's periodic acid routine (PAS) 11
 Schistosoma 569
 Schistosoma haematobium 573
 Schistosoma japonicum 573
 Schistosoma mansoni 573
 Schistosomal infestations types of 573
 Schistosomiasis 573-575
 clinical manifestations of 573-574
 experimental studies in 573
 laboratory findings in 574
 portal hypertension in 283
 stages of 573
 structural alterations in 574-575
 granuloma formation 575

Schistosomiasis - structural alterations in nonspecific reactive hepatitis 575
 pipestem cirrhosis 575
 septal cirrhosis 575
 Schlesinger reaction 73
 Schlesinger test for determination of fecal urobilinogen 363
 Schmidt test for determination of fecal urobilinogen 363
 Schoenheimer Sperry method for determination of serum cholesterol 349
 Sclerosis infantile 518-519
 Screening tests 667
 Secretin 83
 Secretory granules 12, 21
 Secretory pressure of liver 113
 Sedation in acute viral hepatitis 426
 Sedimentation rate in acute viral hepatitis 425
 Segments of liver 162 163
 Selenium 398 593
 Senecio, 396 400 516 519 593
 Senegalese tube 291
 Septal bile ducts 103
 Septum formation central in chronic passive congestion 269
 in reported toxic injuries 269
 in fatty metamorphosis 269-270
 mechanism of 268 269
 peripheral 269
 primary 266 269-270 278
 in schistosomiasis 575
 Septum 255 261
 types of transforming fatty liver into cirrhosis 270
 Serine 28
 urinary excretion of 45
 Serous hepatitis 151
 Serum normal color of 199
 of patients with viral hepatitis cytotoxic effects of in tissue cultures 737
 specific gravity of estimation of 315
 Serum albumin 18
 determination of 318-319
 evaluation of 319
 methods of Howe method 318
 immunologic methods 318
 salting out procedures 318
 specific gravity methods 318
 Wolfson and Cohn method 318
 physiologic basis of 318
 results of 318-319
 reduction of in cirrhosis 281
 Serum albumin level 238 319
 in acute hepatitis 319
 in chronic hepatic diseases 319
 in experimental liver damage 319
 in hepatic disease 319
 in human liver disease 42
 normal 319
 Serum alkaline phosphatase 46-49

Serum alkaline phosphatase in biliary obstruction 47-48
 in cirrhosis without jaundice 48
 determination of 340-342
 evaluation of 342
 methods of 340
 Bodansky 340
 King and Armstrong 340
 physiologic basis of 340
 results of 340-342
 in carcinoma metastases to liver 342
 in cholestasis 341
 in cirrhosis 341
 in granulomatous processes 341-342
 in healthy children 341
 in hepatic abscesses 342
 in hepatic failure 342
 in hepatitis 341
 in normal persons 341
 in Paget's disease 341
 in primary and secondary bone tumors 341
 in rickets 341
 in sarcoidosis 342
 in starvation 341
 in tuberculosis 342
 in tumors 342
 elevation of in tumor metastases 193
 excess extrahepatic origin of 48
 hepatic origin of 48
 origin of in hepatobiliary diseases 48
 excretion of 47
 formation of hepatic site of 48-49
 in hepatic damage 48
 in infectious hepatitis 48
 in ligation of hepatic vein 48
 origin of 47
 in primary and metastatic carcinoma of liver 48
 Serum amino acids 337
 Serum ammonia 217
 Serum amylase (see Amylase)
 Serum bile acids determination of methods of 365
 Pettenkofer reaction 365
 results of 365
 Serum bilirubin 219
 determination of 354-357
 bilirubin tolerance test 356
 evaluation of 357
 icterus index 354
 physiologic basis of 354
 qualitative van den Bergh reaction in 356
 serum bilirubin 357
 total based on diazo reaction 355-356
 results of 355-356
 in experimental animals 355-356
 in extrahepatic biliary obstruction 355
 in jaundice 355
 normal values 355
 technique of procedure in 355
 reagents for 355

- Serum bilirubin 257
 Serum changes in hepatic-cell
 d generation 215-217
 bilirubin and bile salts 217
 carbohydrate metabolism 225
 enzymes 217
 fat metabolism 215
 minerals 217
 protein and nitrogen metabo-
 lism 216-217
 Serum chloride 219
 Serum chloride 217
 Serum cholesterol 36-37
 biliary obstruction 36
 determination of 349-352
 evaluation of 352
 methods of 349-350
 Lieberman-Burchard reac-
 tion 349
 Seliwanoff's test 349
 method 349
 technique in apparatus for
 350
 procedure in 350
 reagents for 349-350
 physiologic basis of 349
 results of in cholesterol
 esters 351-352
 in total serum cholesterol
 350-351
 in cholestasis 350-351
 in hepatocellular dam-
 age 351
 in nonhepatic disorders
 350
 in normal persons 350
 effect of bile acids on 36
 effect of cholestasis on 35
 normal range of 36
 sources of 36
 Serum cholinesterase 217
 Serum citrate determination of
 347
 Serum coagulability reaction Welt-
 man 333
 Serum electrolytes and minerals
 determination of 367
 Serum esterase 48-50
 determination of 342-343
 evaluation of 343
 methods of 342
 technique in 342-343
 procedure in 343
 reagents for 342-343
 physiologic basis of 342
 results of 343
 clinical history of 50
 relation of to cancer 50
 in clinical hepatic failure 50
 after liver resection 50
 in pregnancy 50
 relation of to albumin 50
 to alkaline phosphatase 50
 Serum gamma globulin elevation
 in liver disease 100
 Serum gamma globulin formation
 increased 241
 Serum gamma globulin level in
 cirrhosis 99
 and cytoplasmic basalophilia of
 Kupfer cells correlation
 between 100
 Serum gamma globulin level
 in viral hepatitis 39
 Serum globulin total 321-322
 Serum glutamic-oxalacetic amino-
 acidase 736
 Serum glutamic-oxalacetic trans-
 aminase 50
 Serum histamine levels relation of
 to degree of portal 238
 Serum hyaluronidase inhibitor
 217-239
 Serum iron determination of 367
 Serum iron level 217
 in acute hepatitis 61
 in differential diagnosis of jaun-
 dice 738
 relation of liver to 61
 in viral hepatitis 736
 Serum lactate determination of
 347
 Serum lipid fractions ratios of 352
 Serum lipid total determination
 of 347-348
 method of 348
 technique in procedure
 in 348
 reagents for 348
 standardization 348
 physiologic basis of 347
 results of 348
 Serum mucoproteins determina-
 tion of evaluation of 334
 methods of 334
 physiologic basis of 334
 results of 334
 in hepatic disorders 334
 normal 334
 in secondary biliary cirrho-
 sis 334
 Serum neutral fat determination
 of 345
 Serum phospholipid-cholesterol re-
 lation 235
 Serum phospholipids 34
 amount of 34
 determination of 345-349
 evaluation of 349
 methods of 345
 physiologic basis of 348
 results of 345-349
 sources of 34
 Serum potassium 217
 Serum potassium levels 223
 in cirrhosis 59
 in hepatic disorders 59
 Serum protein alterations in cir-
 rhosis 281
 Serum protein fractions 315-322
 Serum protein reactions nonspe-
 cific 323-332
 Serum protein fractions ratios of
 316-318
 half-life of 318
 total determination of 315-316
 evaluation of 316
 methods of 315-316
 biuret reaction 315
 by falling-drop appar-
 atus 315
 by flotation in copper sul-
 fate solution 315
 Serum proteins total determina-
 tion of methods of by
 refractive index 315
 by tyrosine method of
 Greenberg 315
 physiologic basis of 315
 in liver disease 316
 normal values for 316
 in obstructive jaundice 316
 protein deficiency in 316
 Serum prothrombin conversion ac-
 celerator (see Factor VII)
 Serum pyruvate determination of
 347
 Serum sodium 217-219
 Serum sodium level in cirrho-
 sis 59
 in hepatic disorders 59
 Serum tripeptidase 50
 Serum vitamin A and hepatic sta-
 min A relation between 55
 Serumucosid 334
 Steroidosteroids excretion of 218
 urinary excretion of in liver
 disease 635-639
 Steroid hormones effect of on hepatic
 fat deposition 645-646
 influence of on liver 645-646
 Sex organs and liver relation be-
 tween 643-646
 Sfil virus 414
 Staphylococcus anaerobic bacteria in
 99
 Steep-liver fluke 57-573
 Sheldon's theory of hemochroma-
 tosis 535-539
 Shock hepatic necrosis from
 482-483
 experimental 483
 functional hepatic changes in
 482-483
 human 483
 Shunt portacaval 93-99
 splenorenal 99
 surgical in portal hypertension
 736
 (See also Venous shunt opera-
 tions)
 Sickle-cell anemia 491
 clinical manifestations of 491
 erythrophagocytosis in 99
 structural alterations in 491
 sickle cell crisis 491
 Siderophilin 59-61
 Siderosis 532-535
 endogenous 534
 exogenous 534-535
 nutritional 534-535
 clinical features of 534
 structural alterations in
 534-535
 portal cirrhosis on blood ad-
 ministration 534
 pathogenesis of 534-535
 transfusion 532-539
 Silex fibrosis 286
 Silica impregnations for demon-
 strating repeating fin recticulum
 fibers 11
 Silvestri-Cordis syndrome 644
 Sinusoidal blood flow variations
 in throughout lobule 125

- Sinusoidal circulation impairment
of by fat laden cells 254
- Sinusoids 94-102
alterations of 583
arterial 125
basement membrane of 94
cavernous dilatation of 645
hepatic functional characteris-
tics of 96-102
structural characteristics of
94-96
lining of 94
peripheral 130
radial 130
specific permeability of 96-97
width of 94
- Skeletal system and liver relation
between 631-632
- Skin pruritus 644
- Skin tests for viral hepatitis 415
- Smith test for determination of
bilirubin in urine 358
- Snapper 542
- Sodium 58-59
absent from urine in ascites 294
in anoxia 59
in bile 81
content of in liver 58
in cytoplasm 12
determination of 367
in hepatic disorders 59
and hyperpotasemia 59
increased tubular reabsorption
of 294
- Sodium bilirubinate 70
- Sodium dehydrocholate 82
effect of on hepatic arterial
blood flow 141
for flushing of ducts 84-85
for nonsurgical removal of he-
patic stones 84-85
- Sodium restriction is therapy for
ascites 296
- Sodium retention in ascites 294-
295
- Sodium space of body in cirrhosis
-94
- Sodium syndrome low 296
- Space occupying lesion recogni-
tion of 666
- Species of Disse 149
in autopsy specimens 174
periportal 96
- Spasm as cause of extrahepatic
biliary obstruction 193
- Spathnotchen 443
- Sphincter choledochus 110
- Sphincter of Oddi 108-110
functions of 116-117
and gallbladder interrelation
between 117-119
nerve supply of 153
resistance of 113
spasm of 298
bile salt administration 298
cholecystokinin in 298
colic after cholecystectomy
298
dilatation of duct by pressure
of 30 cm water 298
pilocarpine 298
producing jaundice 299
- Sphincters arterial 125
in hepatic artery system 146
hepatic vein (see Hepatic vein
sphincters)
outlet in venules 134
in portal system 146
portal vein 130
- Spider nevus in clinical hyperes-
trogenism 644-645
- Spinal cord transection 653
- Spinal fluid bilirubin in 198-199
urobilinogen in 199
- Splanchnic blood flow estimated
137
- Splanchnic nerves 152
section of 83
sympathetic fibers from 117
- Splanchnic oxygen consumption
146
after epinephrine 146
total 139
- Splanchnic removal ratio of bac-
teria 99
- Splanchnic section pain of biliary
pressure abolished by 113
- Spleen circulation through 287
function of effect of portal hy-
pertension on 289
gross appearance of 287
and hematopoietic system rela-
tion of liver to 623-629
histologic alterations in 287
289
influence of on liver 623
influence of liver on 623
and liver parallel effect on
623-624
normal 287
in portal hypertension 287 289
size of 287
structure of effect of portal hy-
pertension on 287 289
- Splenectomy 290 291 623
- Splenic artery ligation of 291
- Splenic changes pathogenesis of
289
- Splenography intraperitoneal por-
tal 292
preoperative percutaneous 292
- Splenomegaly obstructive 287
- Splenoportography 619
in intrahepatic portal hyperten-
sion 736
- Splenorenal anastomoses 131
- Splenorenal shunt 291
- Sprue 632
- Stuns 10 11
bile canaliculus 11
carbohydrate Best's carmine
21
PAS 11
connative blue 10-11
Mallory's aniline blue 10
Masson's trichrome 10
silver impregnations 11
Van Gieson's picofuchsin 10
fat oil red "O" 11
sulphur III 11
Grams 11
Gomori's III
Gram 11
Lemaitre's eosin 10
- Stains nucleic acid 11
methyl green pyronin 11
picroline methylene blue 10
- Staligmometry 366
- Standard curves 3-4
- Stirling's law of edema formation
293
- Starvation -7 29 493 500
enzymes in 46
liver fat in 32
- Stasis in cholecystitis 307
- Steatosis 251
- Stefanni 219
- Stellate cells 96
- Stellate nevi 644
- Stenosis from inflammation in
neighboring organs as cause
of extrahepatic biliary obstruc-
tion 191 193
- Stercobilin 73 78
- Stercobilinogen 73 78
- Steric transformation 68
- Steroid hormones 67
- Steroids transformation of 68
- Stilbamidine 396
- Stilbesterol 393 643
- Stone formation 299
causes of 300-301
alteration of bile 300
biliary stress 300-301
metabolic tones 300
stones following inflamma-
tion 301
factors in interrelation of 301
- Stones bilirubin 300
as cause of extrahepatic biliary
obstruction 190-191
in terminal portion of cystic
duct 190
expulsion of into adherent por-
tion of intestine 303
into peritoneal cavity causing
perforation 303
following inflammation 301
impaction of 303
luminated 300
metabolic 300
mixed cholesterol pigment
calcium 300
mullerry 300
pigment calcium 300
pure bilirubin 300
cholesterol 300
earthly 300
shape and constitution of 300
silent 303
- Storage fat 23
- Streamlines of flow 734
- Streptococcus hepatitis 407
- Strick's hepatic response to 654-
655
- Structures 249
as cause of extrahepatic biliary
obstruction 191
from choledocholithiasis 191
congenital of portal vein 286
from decubital ulcers 191
in hepatic duct 191
primary of common duct 191
in spontaneous benign stenosis
191
- Stricture of liver 154-156
- Strongyloides 568

[illegible]

Tests as alarm signals 664
in animal experiments 663-669
with large animals 668-669
cats 668
dogs 668
monkeys 668
rabbits 668
with small animal mice 669
rats 669
biologically false reactions in
positive 669
significant of 662
false positive results in 661
662
in hospital control 661
in normal persons 661
in patients with hepatic
disease 661-662
general uses of 668-669
minimal number of determin-
ations for routine study
663
in infancy and childhood 668
and in autopsy application of
as a ciliary procedure in
clinical problems 664-669
in histology of 661
results of physiological variations
in bile 662
diet 662
menstruation 662
pregnancy 662
selection of 662-663
leptocyst 663
her problem of Watson 662
sensitivity of 663-664
significance of 664
showing hepatic-cell degenera-
tion 664
of value in surgical management
668
Tetracycline 400
Tetraiodoporphyrin 374
Tryptophan pigment 73
Thiamine 26 58
and choline deficient diet 57
effect of on hepatic fat 57
for correcting malnutrition func-
tion of liver 57
intestinal absorption of 58
Thiamine phosphorylation 23
Thiamine pyrophosphate 25
in blood 58
in urine 58
Thyroid 30
Thioacetamide 398 399
Thioctic acid 25
Thiol bond 25
Thiocylic acid 402
administration and evaluation
93
Thionin 398 398 399
Thiolate on morphology of degene-
ration 89
Thiozine 404
Thorium 657
Thorium iodide in phagocytosis
94
Thrombostasis 377
Thrombin 26 495
Thrombin deficiency 57
Thrombin deficient diets 78
Thrombolytic therapy 58

Thrombocytes effect of hemato-
 priic system on 628
 Thrombocytopenia 289 290 628
 Thrombophlebitis migrans 115
 ceral 284
 Thromboplastin 219 221
 The sinus of branches of portal
 vein in liver 141 142
 disseminated platelet 583
 of major hepatic veins portal
 hypertension 119 284
 portal vein 284-286
 causes of 285-286
 clinical features of 285
 splenic vein 285
 spontaneous portal vein 141
 Thymol flocculation 330
 Thymol turbidity test 239 325-
 330 416
 evaluation of 329
 method of 329
 — oral lipid tolerance test 324
 physiologic basis of 328
 effect of lipids 328
 effect of serum proteins 328
 factors in diagnosis 329
 results of in chronic liver
 cirrhosis 329
 in cirrhosis 329
 in disseminated lupus erythe-
 matosus 329
 in extrahepatic biliary obstruc-
 tion 329
 in hepatitis 329
 screening blood donors
 39
 in infectious mononucleosis
 329
 in kala-azar 329
 in lymphopathia venereum
 329
 in malaria 329
 in multiple myeloma 329
 normal 329
 in normal fever 329
 in rheumatoid arthritis 39
 This 31
 influence of on liver 483-484
 effect on hepatic structure
 484
 effect of hyperthyroidism
 484
 effect on regeneration 483
 metabolic effects 483
 Thyroid crisis 485
 Thyroid extract and regeneration
 93
 Thyroid gland influence of liver
 on 484
 normal and liver relation be-
 tween 483-484
 Thyroidectomy 483
 Thyrotoxicosis hepatic conges-
 tion in 483-485
 hepatic injury in manifestations
 of 484-485
 laboratory findings in 485
 structural alteration in
 485
 biopsy findings 485
 types of cirrhosis 48-

- Thyrotoxicosis hepatic injury in
 manifestations of therapeutic considerations in
 485
 thyroid crisis 485
 Thyroxine 34
 Tibione 402
 Tissue bilirubin 195
 green hue in 199
 Tissue breakdown products 393-399
 Tissue changes associated with
 tumor formation 597-599
 Tissue culture of liver 88-734
 Tissue spaces and lymphatic vessels 149-151
 Tissues injured bile pigment in 199
 Tobacco dislike for 119
 Tocopherol 55
 Tolerance tests 313
 Toluylenediamine 179-196-396
 Toluylenediamine hemolysis 183
 Tonus rhythm in gallbladder 113-114
 Tovermia intestinal 223
 Toxic changes in hemolytic disease of the newborn 489
 Toxic hepatic injury 391-412
 allergic cholangiolitis 403-404
 classification of 391
 experimental 391-398
 human etiologic factors in 398-403
 nonspecific reactive hepatitis 404-407
 Toxic hepatic necrosis 407-412
 acute yellow atrophy 411
 cirrhotic transformation 411
 clinical course of 405
 disturbances of circulation in 736
 histologic alterations in autopsy specimens 408-411
 interference with metabolism of hepatic cells in 736
 macroscopic changes in 408
 postoperative toxic hepatitis 411-412
 structural changes of in biopsy specimens 408
 Toxic injury human etiologic factors in 398-403
 endogenous factors 398-399
 bacterial toxins 398
 blood transfusions 399
 hormonal factors 399
 intestinal toxins 398
 tissue breakdown products 398-399
 exogenous factors 399-403
 anesthetics 401
 antibiotics 402
 anticonvulsants 402
 antituberculous drug 402
 carbon tetrachloride 399-400
 hepatic side reactions 402
 inorganic poisons 400
 metals 400-401
 other organic compounds 401
 Toxic injury human etiologic factors in exogenous factors other organic solvents 400
 plant poisons 400
 sulfonamides 401-402
 viral hepatitis mistaken for toxic reactions 402-403
 (See also Toxicity)
 Toxic reactions viral hepatitis mistaken for 402-403
 Toxic substances bypassing liver through collaterals 223
 Toxicity absolute 399-400
 clinical manifestations of 399
 structural alterations in 399-400
 relative 400-401
 Toxins bacterial 393
 intestinal 398
 Toxocara 568
 Toxocara canis 739
 Transaminase 736
 in laboratory animals 736
 in metastatic tumor in liver 736
 Transaminase enzymes 26
 Transamination 26
 Transformation tests 367-370
 Transformations 67-69
 steric 68
 Transmethylation 27-38
 effect of vitamin B₁₂ on 53
 Trauma as cause of hepatic infarction 145
 complications of abscesses 655
 biliary peritonitis 655
 cyst formation in liver 655
 effect of necrotic liver tissue 655
 foreign bodies in biliary passages 655
 traumatic fistulas 655
 functional changes in 654-655
 medicolegal aspects of 655
 severe not involving liver 655
 types of from nonpenetrating injuries 654
 from penetrating wounds 654
 from rupture of liver 654
 Traumatic hepatic injury 654-655
 Trematodes 572-573
 Trinitris 242
 Tricarboic acid cycle of Krebs 25-26
 Trichomonas hominis 572
 Triiodine 402
 Trichyletholone lipotropic activity of 38
 Trimethylamine 735
 Trinitrotoluene (TNT) 396-401
 Trinitrotoluene intoxication 411
 Tropical juvenile cirrhosis 519
 Tropical liver abscess 570
 Tropical malnutrition 516-518-519
 administration of animal protein in 516
 canceroma in 516
 etiologic considerations in 516
 geographical considerations in 516
 Trypan blue 85-102-396
 Trypanosomiasis 439
 Tryptophane 26-57-490
 urinary excretion of 45
 Tubercle epithelioid 552
 hepatic development of 555
 development of fibrosis 555
 histologic differential diagnosis of 555-556
 structural characteristics of 555-556
 Tubercle bacilli 11
 Tuberculous hepatic 556
 Tuberculosis 241-551
 biopsy specimens of 553
 canalicular 556
 and cirrhosis 553-555
 and hepatic injury relation between 556
 hepatic reaction in of other organs 552-555
 clinical and laboratory findings in 552
 structural alterations in 552-555
 cirrhosis and tuberculous 555-555
 fatty metamorphosis 555
 liver biopsy in 739
 miliary 551-552
 diagnostic significance of 552
 laboratory findings in 551
 miliary necrosis 552
 structural alterations in 551-552
 histologic changes 551-552
 cavitation necrosis 552
 epithelioid tubercles 552
 histiocyte or reticuloendothelial nodules 552
 nonspecific reactive hepatitis 551
 macroscopic appearance 551
 Tularemia 564-565
 Tumors 47
 adrenal rest 616
 benign 599
 benign epithelial of biliary tract 592
 carcinoid 616
 as cause of extrahepatic biliary obstruction 189-190
 intrinsic 189
 metastatic 189-190
 primary surrounding bile ducts 189
 extension of, 609-610
 centrifugal growth 610
 distant metastases 610
 peritoneosidal extension 610
 venous spread 610
 formation of tissue changes associated with 597-599
 granulosa cell 645
 metastatic in liver 616-620
 clinical features of 617-619
 clinical significance of 617
 hepatomegaly as presenting feature of 617
 punch in 617-619
 laboratory findings in 619
 newer diagnostic methods in 619-620

Tumors metastatic in liver newer diagnostic methods in administration of radioiodinated human serum albumin 619
liver biopsy 60
peritoneoscopy 620
splenoportography 619
tumor cells found in ascitic fluid 620
routes of invasion of 617
structural alterations in 619
therapy for 620
types of 616-617
neurogenic 616
nephthelial of liver and biliary tract 616
portal hypertension in 284
and regeneration after partial hepatectomy 47
teratoid 616
Turbidity standards 324
barium sulfate 3-4
Turbidity test 323-33-
dilution 330
thymol (see Thymol turbidity test)
zinc sulfate- (see Zinc sulfate-turbidity test)
Typhoid bacillus in bile 82
Typhoid fever 241 407 584
Typhoid nodule intralobular proliferation in 102
Typhus 407 584
Tyrosine 25 45 219 338
urinary excretion of 45
Tyrosinase 50

U

Ulcerative colitis 631-632
cirrhosis in 631
clinical and laboratory findings in 631
pathogenesis of 631-632
structural alterations in 631
Ultrafiltration 12 733
Ultra violet microscopy for nucleic acid 12
Ultraviolet spectrophotometry 16
Umbilical sepsis in neonatal period 407
Umbilical vein 131 133 187
perforation of 131
Undernutrition hepatic brown atrophy from 503-504
Uranuminantate 396
Urea 223
bile 81
metabolism of 27
Urea clearance 649
Ure formation 44
Uremic component 223
Urethra 396 401
Uric acid 27 45 339
in bile 45 81
in blood 45
Uric acid level 217
Urolytic enzymes 337-338
chromatography of 337-338
Fanconi's syndrome 338
Wolff's distal 338

Urinary amino acids evaluation of 333
microbiologic determinations of 338
Mill's test 338
Tyrosinuria 333
Urinary bilirubin giving direct van den Bergh reaction 78
Urinary coproporphyrins 1218
Urinary estrogens 69
Urinary excretion 45
of bilirubin 77-78
role of bile acids in 78
of Bromsulphalein 85
of urobilinogen 78-79
of urobilin 45
Urinary gonadotropin excretion 218
Urinary acids in (see Bile acids in urine)
chemical changes in 217-218
urobilinogen in (see Urobilinogen in urine)
Urobilin 70
qualitative tests for 360
Urobilinogen 72 78
Urobilinogen 73 185 187
biliary determination of 36-
363
in blood 78
diagnostic 362
fecal (see Fecal urobilinogen)
in spinal fluid 199
urinary 218 237
urinary excretion of 78-79
in urine determination of 359-
363
excretion of 362
metabolism of 359-361
physiologic basis of in cholestasis 359
in hepatic cell degeneration 359
quantitative tests for 360
quantitative methods of 360-361
culture of 361-362
in biliary obstruction 36-
n hepatitis and cirrhosis 361-362
in other conditions 36-
semiquantitative methods of 360
technique in 360-361
calculation 361
collection of specimens 361
procedure in 361
reagents for 360-361
urobilinogen tolerance test 36-
36-
Urobilinogen group two main components of 361
Urobilinogen tolerance test 362
Urobilinogenuria 185
Uroporphyrins 79

V

Vacuoles fat 11
Vagotomy for biliary pressure 113
Vagotomy 299

Vagus 15-
Vagus nerves 117
Vaginal 26 28 218
urinary excretion of 45
Van Creveld 54-
Van den Bergh 179
concept of transformation of indirect reacting to prompt reacting bilirubin by liver 187
Van den Bergh Aschoff concept of jaundice 181-182
Van den Bergh reaction 734
of bilirubin 76-77 354
biphasic 76
delayed direct 76
direct 76
urinary bilirubin 76 78
indirect 76
qualitative biphasic 356
delayed 356
(See also Diazo reaction of van den Bergh)
Van Gieson's picrofuchsin stain 10
Vascular bleeding of emergency procedures for 290-291
736
ligation 291
Patton tube 291
Sengstaken tube 291
tamponade 290
thromboplastic agents 290
topical application of 290
water 290
esophageal hemorrhage from 133 736
gastric 290
rupture of as cause of hematemesis 290
as cause of melena 290
Vascular anastomosis 735
anastomosis and mesenteric blood 135-138
Vascular disease of liver 579 583
Vascular distribution comparison of in man and rats 147-149
Vascular spasm 644
Vascular structural principle of 135-138
intrahepatic vascular anastomosis and mesenteric blood 135-138
VDM 44 59 294 647
VDM/VEA mechanism 62
Ventral hepatic portal system with portocaval shunts 286
Ventral abdominal wall 131
ventral 133
conducting 127
coronary 127 133
diaphragmatic 133
distributing 127 130
esophageal 133
gastroepiploic 133
hemorrhoidal 133
inferior mesenteric 127
intercalated 133
in mesenteric structure of 133
nephrotic 127
large collecting 133
mesenteric 133
paramesenteric 127
peristaltic 127

- Veins portal** (see Portal vein)
 retroperitoneal 133
 right gastric 133
 splenic 127
 sublobular 133
 superior mesenteric 1-7
 vitelline 165, 166
 (See also Hepatic vein)
- VENI 647**
- Vena cava inferior supradiaphragmatic constriction of** 286
- Venocclusive disease of liver** 518-519
- Venous bruit** (see Venous hum)
- Venous drainage of peribiliary plexus** 130
- Venous hum** 133, 290, 5-3, 603
- Venous shunt operations** 291-292
 and ascites 294
 contraindications to 292
 end to side procedure in 291
 hepatic tests after results of 292
 high protein diets following 292
 indications for 291
 mortality rates in 292
 results of in cirrhosis 292
 in portal vein obstruction 292
 selection of shunt for 292
 by preoperative percutaneous or intraoperative portal splenography 292
 side to side procedure in 291
- Venules** 130
 outlet sphincters in 134
- Verdohemochrome** 72, 75
- Verzar hypolytic theory of** 33
- Viral diseases nonspecific reactive hepatitis in** 407
- Viral hepatitis** 242
 acute (see Acute viral hepatitis)
 allergic reactions in 658
 animal transmission of 415
 in animals 456-457
 antibodies in 415
 carrier state of 415-416
 screening for carriers 416
 virus A carriers 415-416
 virus B carriers 416
 cholestasis in 195-196
 chronic 439-453
 civilian epidemics of 418
 cold or heterophil agglutinins in 415
 epidemics of in military personnel 418
 epidemiology of 418-421
 etiology of 414-418
 immunity to 417-418
 A virus 417
 B virus 417
 differences between A and B viruses 418
 effect of gamma globulin on 417-418
 incidence of in World War II 418
 incubation period of 416-417
 mistaken for toxic reactions 402-403
 portal hypertension caused by 284
 processed blood products in 420
- Viral hepatitis prophylaxis of** 419
 protracted convalescence from Laboratory findings during 451, 453
 when to do liver biopsy 453
 when to permit return to normal activity 451
 residual changes following 737
 seasonal incidence of 418
 serologic reactions in 415
 skin tests for 415
 with spotty necrosis 428-434
 histologic differential diagnosis of 434
 in anicteric hepatitis 434
 histologic variations in 432
 icteric stage of 428-432
 changes in intralobular mesenchyma 430
 changes in portal tracts 430-432
 parenchymal changes in 428, 430
 acidophilic bodies 428, 430
 acidophilic degeneration 4-8
 balloon cells 428
 bile canaliculi alterations 430
 necrosis 428
 nuclear variations 428
 regeneration 430
 morphogenesis of 432, 434
 preicteric stage of 428
 three attacks of 737
 vs toxic hepatitis 453
 transmission of amount of blood necessary for 419
 by blood sucking insects 418
 to human volunteers infectivity of in feces 415
 in nasal washings 415
 in serum 415
 in urine 415
 (See also Virus properties of)
- Virchow** 279
- theory of** 414
- Virus properties of** 414-415
 culture 414
 resistance autoclaving in 414
 beta propiolactone in 414
 cold ethanol fractionation in 414
 disinfectants in 414
 heat treatment in 414
 nitrogen mustard in 414
 storage of plasma at room temperature in 414
 ultraviolet irradiation in 414
 size 415
- Visceral thrombophlebitis migrans** 593
- Viscerotopias** 170
- Visualization contrast** 375
- Vital microscopy** 9-10
- Vitamin A** 52-55, 213
 and adrenal cortical hormone 52
 in animal 52
 carcinogens and 53
- Vitamin A content of in human liver** 53
 in experimental hepatic injury 53
 in fish 53
 in hepatic cells 52
 in hepatic injury 52
 histologic 53
 intestinal absorption of 52
 in Kupffer cells 52, 100-101
 in liver 53-55
 in liver diseases 50
 in malnutrition 50
 in mitochondria 20
 in obstructive jaundice 52
 release of from liver (see Plasma vitamin A)
 after reticuloendothelial blockade 100
 site of in cells 53
 tests concerning 366-367
 tolerance curve of 52
 toxicity of 52
 transport of to liver 52
 variation of with age 53
 in vitamin E deficiency 53
- Vitamin A alcohol** 52
- Vitamin A deficiency** 53
- Vitamin A ester** 52
 and alcohol partition of 733
- Vitamin A esterase** 49
- Vitamin A fluorescence** 53
 distribution of in cell 53
 in hepatic damage 53, 55
 in hypervitaminosis A 53
 normally 53
- Vitamin B complex** 56
 deficiency of and fatty metamorphosis 56
- Vitamin B₁** 27, 57-58
 effect of on transmethylation 58
 and hepatic nucleoprotein 57
 lipotropic activity of 38, 58
 in methylation 38
 and regeneration 93
- Vitamin B₁ deficiency** 58
- Vitamin C** 58
 effect of on excretion of bile pigment 58
 on Golgi apparatus 58
- Vitamin D** 55, 651
- Vitamin E** 55-56
 in biliary obstruction 56
 content of 55
 in liver disease 55-56
 plasma level of 55
- Vitamin E deficiency** 19, 56
 vitamin A in 53
- Vitamin F tolerance curve** 56
- Vitamin K** 56, 220, 237
 and factor VII 43
 hypoprothrombinemia with faulty response to 220
 relation of to prothrombin 43, 220
 requirement of 56
- Vitamin K absorption defect of** 220
- Vitamin K administration in response of prothrombin time to** 336, 337
- Vitamin K deficiency** 56

- Tumors metastatic in liver new r
diagnostic methods in
administration of r
dio-iodinated human
serum albumin 619
liver biopsy 610
peritoneoscopy 620
splenoportography 619
tumor cells found in
ascitic fluid 620
r tests of invasion of 617
structural alterations in
619
therapy for 620
types of 616-617
neurogenic 616
nonneoplastic of liver and biliary
tract 616
portal hypertension in 284
and regeneration after partial
hepatectomy 47
terato 618
Turbidity standards 324
Turbidity sulfate 324
Turbidity test 323-332
turbid 330
thymol (see Thymol turbidity
test)
zinc sulfate—(see Zinc sulfate
turbid test)
Typhoid bacillus in bile 82
Typhoid fever 241 40* 584
Typhoid nodule intralobular
proliferation in 101
Typhus 407 584
Tyrosine 18 45 218 335
urinary excretion of 45
Tyrosinemia 50
- U
- Ulcerative colitis 631-632
curettage in 631
clinical and laboratory findings
in 631
pituitogenesis of 631-632
structural alterations in 631
Ultracentrifugation 12 733
Ultraviolet microscopy for nucleic
acid 12
Ultraviolet spectrophotometry 16
Umbilical sepsis in neonatal period
407
Umbilical vein 131 133 167
perforation of 131
Undernutrition hepatic brown
atrophy from 503-504
Uranium nitrate 396
Urea 223
in bile 81
metabolism of 27
Urea clearance 649
Urea formatin 44
Urea component 223
Urethane 396 401
Uric acid 27 45 339
in bile 45 81
in blood 45
Uric acid 1 217
Urinary amino acids 33-335
chromatographic observations of
in Fenton's syndrome 334
in Wilson's disease 338
- Urinary amino acids evaluation
of 335
microbiologic determinations of
338
Millon test 335
tyrosin 335
Urinary bilirubin giving direct van
den Bergh reaction 78
Urinary coproporphyrins I 218
Urinary estrogens 68
Urinary excretion of 45
of bilirubin 77-78
of bile acids in 78
of bromophenol 85
of urobilinogen 78-79
of urobilin 45
Urinary gonadotropin excretion
218
Urine bile acid in (see Bile acids
in urine)
chemical changes in 217-218
urobilinogen in (see Urobilinogen
in urine)
Urobilin 70
qualitative tests for 360
Urobilin 132 72 78
Urobilinogen 70 73 185 187
bilirubin determination of 362-
363
in blood 78
detention of 362
fecal (see Fecal urobilinogen)
in spinal fluid 199
urinary 218 237
urinary excretion of 78-79
in urine determination of 359-
363
evaluation of 362
methods of 359-361
physiologic basis of in
cholestasis 359
in hepatic cell degenera-
tion 359
qualitative tests for 360
quantitative methods of
360-361
results of 361-362
in biliary obstruction
362
in hepatitis and cirrhosis
361-362
in other conditions 362
semiquantitative methods
of 360
technique in 360-361
calculation 361
collection of specimens
361
procedure in 361
reagents for 360-361
urobilinogen tolerance test
362
Urobilinogen group titrimetric com-
position tests of separation of 79
Urobilinogen tolerance test 362
Urobilinogenuria 185
Uroporphyrins 79
- V
- Vaginal sepsis 21
Vagotomy for biliary pressure 113
Vagotomy 299
Vagus 152
Vagus nerves 117
Valine 26 28 218
urinary excretion of 45
Van Creveld 542
Van den Bergh 179
concept of transformation of
indirect reacting to prompt
reacting bilirubin by liver
187
Van den Bergh Aschoff concept of
jaundice 181-182
Van den Bergh reaction 734
of bilirubin 76-77 304
biphasic 76
delayed direct 76
direct 76
urinary bilirubin giving 78
indirect 76
qualitative biphasic 356
delayed 356
(See also Diazo reaction of an-
den Bergh)
Van Gieson's picrofuchsin stain 10
Vascular bleeding of emergency
procedures for 290-291
736
ligation 291
Patton tube 291
Sengstaken tube 291
tamponade 290
thromboplastic agents 290
topical application of ice
water 290
esophageal hemorrhage from
133 736
gastric 290
rupture of as cause of lemate-
mesis 290
as cause of melanoma 290
Vascular stomatosis 735
intestine atrophic and mixing of
blood 135-136
Vascular diseases of liver 579-593
Vascular distribution comparison
of in man and rats 147-148
Vascular spiders 644
Vascular tree structural principle
of 135-136
extrahepatic vascular anasto-
moses and mixing of blood
135-136
VDM 44 59 294 647
VDM mechanism 64
Vena ligata hepatic in dogs
with portocaval shunts 286
Vessels in abdominal wall 131
ventral 133
conduct 127
coronary 127 133
diaphragmatic 133
distributing 127 130
esophageal 133
gastroepiploic 133
hemorrhoidal 133
inferior mesenteric 127
intercalated 133
microscopic structure of 133
intraligamentary 127
lymphatic collecting 133
microscopic structure of 133
pyramidal 127
pulsating umbilical 127

- Veins portal (*see* Portal vein)
 retroperitoneal 133
 right gastric 133
 splenic 1-7
 sublobular 133
 superior mesenteric 127
 vitelline 165, 166
 (*See also* Hepatic vein)
- VEM 647
- Vena cava inferior supradiaphragmatic constriction of 286
- Venocclusive disease of liver 518-519
- Venous bruit (*see* Venous hum)
- Venous drainage of peribiliary plexus 130
- Venous hum 133, 290, 523, 603
- Venous shunt operations 291-292 and ascites 294
 contraindications to 29-
 end to side procedure in 291
 hepatic tests after results of 292
 high protein diets following 29-
 indications for 291
 mortality rates in 292
 results of in cirrhosis 292
 in portal vein obstruction 292
 selection of shunt for 292
 by preoperative percutaneous or intraoperative portal splenography 292
 side to side procedure in 292
- Venules 130
 outlet sphincters in 134
- Verdohemochrome 72, 75
- Verzar hypolytic theory of 33
- Viral diseases nonspecific reactive hepatitis in 407
- Viral hepatitis 242
 acute (*see* Acute viral hepatitis)
 allergic reactions in 353
 animal transmission of 415
 in animals 456-457
 antibodies in 415
 carrier state of 415-416
 screening for carriers 418
 virus A carriers 415-416
 virus B carriers 416
 cholestasis in 195-196
 chronic 439-453
 civilian epidemics of 418
 cold or heterophil agglutinins in 415
 epidemics of in military personnel 418
 epidemiology of 418-421
 etiology of 414-418
 immunity to 417-418
 A virus 417
 B virus 417
 differences between A and B viruses 418
 effect of gamma globulin on 417-418
 incidence of in World War II 418
 incubation period of 416-417
 mistaken for toxic reactions 402-403
 portal hypertension caused by 284
 processed blood products in 420
- Viral hepatitis prophylaxis of 419
 protracted convalescence from laboratory findings during 451, 453
 when to do liver biopsy 453
 when to permit return to normal activity 452
 residual changes following 737
 seasonal incidence of 418
 serologic reactions in 415
 skin tests for 415
 with spotty necrosis 428-434
 histologic differential diagnosis of 434
 in amniotic hepatitis 434
 histologic variations in 432
 icteric stage of 428-432
 changes in intralobular mesenchyma 430
 changes in portal tracts 430-432
 parenchymal changes in 428, 430
 acidophilic bodies 428, 430
 acidophilic degeneration 428
 balloon cells 428
 bile canaliculi alterations 430
 necrosis 428
 nuclear variations 428
 regeneration 430
 morphogenesis of 432-434
 preicteric stage of 428
 three attacks of 737
 vs toxic hepatitis 453
 transmission of amount of blood necessary for 419
 by blood sucking insects 418
 to human volunteers infectivity of in feces 415
 in nasal washings 415
 in serum 415
 in urine 415
 (*See also* Virus properties of)
- Virchow 179
 theory of 414
- Virus properties of 414-415
 culture 414
 resistance autoclaving in 414
 beta propionolactone in 414
 cold ethanol fractionation in 414
 disinfectants in 414
 heat treatment in 414
 nitrogen mustard in 414
 storage of plasma at room temperature in 414
 ultraviolet irradiation in 414
 size 415
- Visceral thrombophlebitis migrans 593
- Visceropsiosis 170
- Visualization contrast 375
- Vital microscopy 9-10
- Vitamin A 52-55, 213
 and adrenal cortical hormone 52
 in animals 5-
 carcinogens and 53
- Vitamin A content of in human liver 53
 in experimental hepatic injury 53
 in fish 53
 in hepatic cells 52
 in hepatic injury 52
 histologic 53
 intestinal absorption of 52
 in Kupffer cells 52, 100-101
 in liver 53-55
 in liver diseases 53
 in malnutrition 53
 in mitochondria 20
 in obstructive jaundice 53
 release of from liver (*see* Plasma vitamin A)
 after reticuloendothelial blockade 100
 site of in cells 53
 tests concerning 366-367
 tolerance curve of 52
 toxicity of 5-
 transport of to liver 52
 variation of with age 53
 in vitamin E deficiency 53
- Vitamin A alcohol 52
- Vitamin A deficiency 53
- Vitamin A ester 5-
 and alcohol partition of 733
- Vitamin A esterase 49
- Vitamin A fluorescence 53
 distribution of in cell 53
 in hepatic damage 53, 55
 in hypervitaminosis A 53
 normally 53
- Vitamin B complex 56
 deficiency of and fatty metamorphosis 56
- Vitamin B₁ 27, 57-58
 effect of on transmethylation 58
 and hepatic nucleoprotein 57
 lipotropic activity of 38, 58
 in methylation 38
 and regeneration 93
- Vitamin B₁ deficiency 58
- Vitamin C 58
 effect of on excretion of bile pigment 58
 on Golgi apparatus 58
- Vitamin D 55, 651
- Vitamin E 55-56
 in biliary obstruction 56
 content of 55
 in liver disease 55-56
 plasma level of 55
- Vitamin E deficiency 19, 56
 vitamin A in 53
- Vitamin E tolerance curve 56
- Vitamin K 56, 220, 237
 and factor VII 43
 hypoprotrombinemia with faulty response to 220
 relation of to prothrombin 43, 56
 requirement of 56
- Vitamin K absorption defect of 220
- Vitamin K administration response of prothrombin time to 337
- Vitamin K deficiency 56

Vitamin K tolerance test 337
 Vitamins administration of 501
 in bile 81
 Vitelline veins 165 166
 Vitelline vesicles 165
 Von Cierke 542

W

Walden enzyme 31
 Walden from porphyrin 79
 Water in regenerating liver 92
 Water content of hepatic cell 82
 Water metabolism 62 367
 influence of liver on 62
 physiologic basis of 367
 Water retention 367
 in ascites 294
 Water tolerance tests 367
 Watson 151
 liver profile of 662
 method of for determination of
 urobilinogen in urine 360
 Wear and tear pigment 11 19
 Wedg pressure 253 736
 Weight of liver 163
 Wels disease 457-458
 bilirubin in 199
 functional alterations of liver in
 457-458
 stages of 457
 structural alterations of liver in
 458
 Weltmann serum-coagulation reac-
 tion 333
 Wernicke's hemorrhagic polyen-
 cephalitis and cirrhosis 56

Wilson's disease 45 338 540-542
 339
 central nervous system involve-
 ment in 542
 clinical manifestations and labora-
 tory findings in 542
 etiology of 541-542
 hemociduria 541-542
 disturbance of copper metabolism
 in 541
 peptiluria 542
 form of 540-541
 hepatic involvement in 542
 structural alterations in 542
 therapy for 542
 Wirsung duct of 632
 With therapy of on jaundice 181
 Wolfson and Cohn method of de-
 termining of serum albumin
 315

X

Xanthelasma 235 467
 Xanthine oxidase 16 45 46 51
 217
 and folic acid 57
 Xanthochromia in icterus neonata-
 torum 199
 Xanthomas 190 467
 differential diagnosis of cholesta-
 stasis 467
 skin 235
 Xanthomatous stage of atresia 171
 Xanthopsia 198
 Xanthorubin 199
 X-ray irradiation effect of on
 DNA 21
 and PNA 18

X-ray visualization of gallbladder
 and bile ducts 86

Y

Yellow atrophy acute 212 411
 414
 Yellow fever hepatitis 455-456
 clinical manifestations of 455-
 456
 laboratory findings in 456
 structural changes in 456
 Yellow fever vaccine potency
 419-420
 Yolk sac 165

Z

Zaferin infarct 141 142
 Zenker solution 10
 Zinc 62
 in bile 81
 Zinc sulfate test 239
 Zinc sulfate-turbidity test 324-
 326
 buffered test solution in 35
 dilution of 325-326
 physiologic basis of 324-325
 procedure in 325
 reagents for 325
 results of in acute hepatitis 325
 in cirrhosis 325
 in extrahepatic biliary obstruc-
 tion 325
 normal 325
 technique of 325
 Ziegler's test 450

Vitamin A-tolerant test 337
 Vitamin administration of 501
 in bile 81
 Vitelline veins 165 166
 Vitelline vessels 165
 Von Cierke 542

W

Walden enzyme 31
 Waldenstrom porphyria 79
 Water in regenerating liver 92
 Water content of hepatic cell 62
 Water metabolism 62 367
 influence of liver on 62
 physiologic basis of 367
 Water retention 367
 in ascites 294
 Water tolerance tests 367
 Watson 181
 liver profile of 662
 method of for determination of
 urobilinogen in urine 360
 Wear and tear pigment 11 19
 Wedge pressure 283 736
 Weight of liver 163
 Wells disease 457-458
 functional alterations of liver in
 457-458
 stages of 457
 structural alterations of liver in
 458
 Weltmann serum-coagulation reac-
 tion 333
 Wertheim's hemorrhagic polioen-
 cephalitis and cirrhosis 58

Wilson's disease 45 319 540-542
 739
 central nervous system involv-
 ement 542
 clinical manifestations and labo-
 ratory findings in 542
 treatment of 541-542
 jaundicedness 541-542
 disturbance of copper metabo-
 lism 541
 peptiduria 542
 forms of 540-541
 hepatic involvement in 542
 structural alterations in 542
 therapy for 542
 Wirsung duct of 632
 With theory of on jaundice 181
 Wolfson and Cohn method of de-
 termination of serum albumin
 318

X

Xanthelasma 239 467
 Xanthin, dose 16 45 46 51
 217
 and folate acid 57
 Xanthochromia in icterus neonata-
 rum 199
 Xanthomas 170 467
 differential diagnosis of cholan-
 gitic cirrhosis with 467
 skin 235
 Xanthomatous stage of atresia 171
 Xanthopsia 198
 Xanthorubin 199
 X-ray irradiation effect of on
 DNA 21
 and PVA 18

X-ray visualization of gallbladder
 and bile ducts 86

Y

Yellow atrophy acute 212 411
 414
 Yellow fever hepatitis 455-456
 clinical manifestations of 455-
 456
 laboratory findings in 456
 structural changes in 456
 Yellow fever vaccine jaundice
 419-420
 Yolk sac 165

Z

Zahn infarct 141 142
 Zerkow solution 10
 Zinc 62
 in bile 81
 Zinc sulfate test 239
 Zinc sulfate-turbidity test 3-4-
 326
 bull red test solution in 325
 evaluation of 325-326
 physiologic basis of 324-3 5
 procedure in 325
 reagents for 325
 results of in acute hepatitis 325
 in cirrhosis 325
 in extrahepatic biliary obstruc-
 tion 325
 normal 325
 test queue of 325
 Zick gallbladder 450